IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: BRIMONIDINE PATENT LITIGATION	C.A. No. 07-md-1866-GMS

JOINT APPENDIX OF INTRINSIC AND EXTRINSIC EVIDENCE

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JOINT APPENDIX OF INTRINSIC AND EXTRINSIC EVIDENCE

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[45] Date of Patent: Jun. 13, 1995

[54] **AQUEOUS OPHTHALMIC FORMULATIONS AND METHODS FOR PRESERVING SAME**

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[73] Assignee: **Allergan, Inc.**, Irvine, Calif.

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[52] **U.S. Cl.** **424/661**; 514/557; 514/912

[58] **Field of Search** 424/661; 514/557, 912

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[57] **ABSTRACT**

Stabilized chlorine dioxide is a preservative for ophthalmic formulations. The stabilized chlorine dioxide, when employed as a preservative ophthalmic formulations is preferably present in an amount of from about 0.0002 or about 0.002 to about 0.02 weight/volume percent. The aqueous ophthalmic formulations, in addition to the stabilized chlorine dioxide and the water which functions as a vehicle for the formulations, contains an ophthalmically acceptable tonicity component effective to maintain the osmolality of the formulation at least about 200 mOsmol/kg, and a buffer to maintain the pH of the ophthalmic formulation within an acceptable physiological range. A method for preserving aqueous ophthalmic formulations utilizing stabilized chlorine dioxide is also set forth.

18 Claims, No Drawings

AQUEOUS OPHTHALMIC FORMULATIONS AND METHODS FOR PRESERVING SAME

Related Application

This application is a continuation-in-part of application Ser. No. 277,791, filed Nov. 29, 1988. The disclosure of this prior application is hereby incorporated in its entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to preserving ophthalmic formulations or compositions, such as solutions. More particularly it relates to the use of stabilized chlorine dioxide to preserve ophthalmic formulations.

The use of contact lens has become widespread as a replacement for conventional eye glasses because of the improved vision obtained by the wearer or for aesthetic reasons. Contact lenses accumulate microorganisms and cellular debris from the eye. Thus, the lenses must be periodically removed and cleaned to prevent irritation of the eye or infection. Formulations used in lens care must be preserved by some means to interdict introducing microbial contaminants onto contact lenses or into the eye. Disinfecting preparations are part of the regimen indicated for contact lens care.

Numerous ophthalmic formulations have heretofore been used with lenses. The composition of the ophthalmic formulation will often be dictated by the polymeric materials employed in the fabrication of the contact lens. Because of the chemical composition of most ophthalmic formulations, the contact lenses treated, e.g., disinfected, cleaned, soaked, and the like, in such formulations must be rinsed prior to placement in the wearer's eye to prevent irritation of the eye.

Problems have also been encountered in the use of the prior art ophthalmic formulations for the treatment of contact lenses in that such formulations often become contaminated or deteriorate when exposed to the atmosphere once the seal of he formulation container has been broken. Microorganisms and/or other impurities often contaminate the formulation which requires that the formulation be discarded. Thus, there exists a need for aqueous ophthalmic compositions having extended lives. In other words, there is a need for ophthalmic formulations which are effectively preserved without being irritating or otherwise damaging to the eye. It is to such preserved ophthalmic formulations and methods for preserving ophthalmic formulations that the present invention is directed.

Ratcliff U.S. Pat. Nos. 4,696,811 and 4,689,215 disclose the use of stabilized chlorine dioxide for the treatment and prevention of oral disease, for the reduction of malodor, as an anti-plaque agent, an anti-gingivitis and anti-peridontitis agent, as well as a denture soak. These two patents disclose the use of 0.005 percent to 0.02 percent stabilized chlorine dioxide in sterilized water as a contact lens soaking formulation. However, the patents are void of any teaching or suggestion that stabilized chlorine dioxide can be incorporated into an ophthalmic formulation as a preservative for such a formulation. In addition, the patents do not disclose the use of buffer or tonicity components.

Stockel et al U.S. Pat. No. 4,499,077 discloses an antimicrobial composition for soft contact lenses including an oxidizing agent such as an oxyhalogen compound, e.g., stabilized chlorine dioxide, or hydrogen peroxide, and a polymeric germicide, e.g., a quaternary ammonium polymer or an amino and/or imino polymer or salts thereof. Stockel et al U.S. Pat. No. 4,654,208 discloses an antimicrobial composition for contact lenses including an aqueous solution of a germicidal polymeric nitrogen compound and an oxidizing agent, e.g., chlorine dioxide, stabilized chlorine dioxide or hydrogen peroxide, to potentiate the activity of the germicidal polymeric nitrogen compound at low concentrations. The Stockel et al patents characterize the "polymeric germicides" and the "germicidal polymeric nitrogen compounds" as positively charged, nitrogen-containing cationic polymers, such as certain quaternary ammonium polymers and polymeric amino and/or imino compounds, e.g., polydiguanides. Neither of these Stockel et al patents relate to ophthalmic compositions without such positively charged, nitrogen-containing cationic polymers.

SUMMARY OF THE INVENTION

Broadly, the present invention relates to aqueous ophthalmic formulations containing an effective minor amount of stabilized chlorine dioxide to effectively preserve the ophthalmic formulation; a buffer component and a tonicity component. The present ophthalmic formulations are effectively preserved and can be used, e.g., in the contact lens care context, without causing irritation or discomfort to the eyes of the user of the formulations.

In one aspect, the present invention relates to aqueous ophthalmic formulations or compositions, for example, solutions, comprising water, e.g., as a vehicle; an amount, preferably from about 0.0002 or about 0.002 to about 0.02 weight/volume percent, of stabilized chlorine dioxide effective to act as the sole preservative in the formulation; at least one buffer component in an amount effective to maintain the pH of the formulation in the range of about 6.8 to about 8; and at least one tonicity component in an amount effective to maintain the formulation at an osmolality of at least about 200 mOsmol/kg, especially at a tonicity value substantially corresponding to the tonicity value of fluids of an eye. The present ophthalmic formulations preferably include substantially no, i.e., are substantially free of, germicidally effective amounts of any positively charged, nitrogen-containing cationic polymers, for example, the quaternary ammonium polymers, the polymeric amino and/or imino compounds and their salts disclosed in the above-noted Stockel et al patents. More preferably, the present ophthalmic formulations are substantially free of any such positively charged, nitrogen-containing cationic polymers. To provide the ophthalmic formulations with a pH substantially corresponding to the pH of the fluids of the eye, the pH of the ophthalmic formulation can be adjusted, if required, by addition of an acid or a base.

Methods for preserving ophthalmic formulations are also disclosed.

DETAILED DESCRIPTION

Stabilized chlorine dioxide has been found to be effective as a sole preservative in preserving ophthalmic formulations or compositions. Thus, the present formulations include stabilized chlorine dioxide in an amount effective to act as the sole preservative in the formulations. Although one or more other preservatives may be present, it is preferred that the formulations include no other effective preservatives. In a particularly useful

embodiment, the present formulations preferably include no germicidally effective amount of any positively charged, nitrogen-containing cationic polymers, such as those disclosed in the above-noted Stockel et al patents. Still more preferably, the present formulations are substantially free of any quaternary ammonium compounds. Since stabilized chlorine dioxide has been found to be effective as the sole preservative for ophthalmic formulations, the presence of such nitrogen-containing cationic polymers and quaternary ammonium compounds, which can result in eye irritation or discomfort, is not needed.

The preserving amount of stabilized chlorine dioxide incorporated into an ophthalmic formulation (that is, to prevent microbial growth in the formulation) can vary widely but will generally be an amount sufficient to preserve the composition, for example, the physical and/or chemical integrity of the formulation. The presence of stabilized chlorine dioxide enhances, even greatly enhances, or prolongs the useful or shelf life of the present ophthalmic formulations.

The present formulations preserved with stabilized chlorine dioxide can be used in treating or caring for contact lenses made of a wide variety of different materials, such as different polymeric materials, without any substantial degradation of the lenses.

The thus treated or cared for contact lenses, such as lenses cleansed and soaked using an ophthalmic formulation in accordance with the present invention, can often be placed directly into the wearer's eye without the additional requirement of rinsing to remove residual formulation therefrom. Thus, contamination of the treated or cared for lenses can be substantially eliminated prior to placement in the wearer's eye.

Further, an effective disinfectant can be provided which effectively kills microorganisms which may be present on ophthalmic devices, for example, contact lenses. The disinfectant comprises at least 0.02 weight-/volume percent stabilized chlorine dioxide as the disinfecting agent, for example, as the sole disinfecting agent.

The term "stabilized chlorine dioxide" is well known in the industry and by those skilled in the art. Stabilized chlorine dioxide includes one or more chlorine dioxide precursors such as one or more chlorine dioxide-containing complexes and/or one or more chlorite-containing components and/or one or more other entities capable of decomposing or being decomposed in a liquid, preferably aqueous, medium to form chlorine dioxide. U.S. Pat. No. No. 2,271,242 discloses a form of stabilized chlorine dioxide and a method for producing same which can be used as a preservative for aqueous ophthalmic solutions or as a disinfectant for ophthalmic devices. The disclosure of this patent is hereby incorporated in its entirety by reference herein. The manufacture or production of certain stabilized chlorine dioxide products is described in McNicholas U.S. Pat. No. 3,278,447, the disclosure of which is hereby incorporated in its entirety by reference herein. A commercially available stabilized chlorine dioxide which can be utilized in the practice of the present invention is the proprietary stabilized chlorine dioxide of BioCide International, Inc. of Norman, Okla., sold under the trademark Purogene. Other suitable stabilized chlorine dioxide products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Antheium Dioxide by International Dioxide, Inc.

One aspect of the present invention resides in the use of a preserving amount of stabilized chlorine dioxide in aqueous ophthalmic formulations. It has been found that ophthalmic devices contacted with an aqueous ophthalmic formulation containing a preserving amount of stabilized chlorine dioxide and effective amounts of at least one of each of buffer and tonicity components often do not have to be rinsed to remove residual formulation prior to use, e.g., in the eye. Similarly, when such formulations are employed in a regimen of contact lens care, the contact lenses can often be placed in a wearer's eye, without rinsing, without irritation or adverse effects occurring to the tissue of the eye, and without discomfort.

The amount of stabilized chlorine dioxide incorporated in the ophthalmic formulation as a preservative can vary widely provided that such amount effectively prevents microbial growth in the formulation. The amount of stabilized chlorine dioxide included in the formulation is preferably in the range of about 0.0002 or about 0.002 to about 0.02, more preferably about 0.004 to about 0.01, weight/volume percent of the formulation.

In order to provide that the aqueous ophthalmic formulation containing a preserving amount of stabilized chlorine dioxide does not irritate one's eye, it is important that the ophthalmic formulation have a pH value in the range of about 6.8 to about 8, preferably about 7 to about 7.5, and still more preferably so that the pH of the ophthalmic formulation substantially corresponds to the pH value of the fluids in the eye, in particular, the human eye.

To stabilize or maintain the ophthalmic formulation at the desired pH, an effective minor amount of at least one buffer component is incorporated into the ophthalmic formulation. The effective minor amount of buffer component employed to buffer or maintain the formulation at the desired pH can vary widely and depends to a large degree on the particular buffer component employed, as well as the chemical composition of the ophthalmic formulation. However, desirable results have been obtained when the amount of buffering component incorporated into the aqueous ophthalmic formulation to stabilize the formulation at an acceptable physiological pH is in the range of about 0.05 to about 1 weight-/volume percent of the formulation.

Any suitable buffer component can be employed which is compatible with the other ingredients of the ophthalmic formulation, and which does not have deleterious or toxic properties which could harm the eye. Examples of suitable ophthalmically acceptable buffer components include acetate buffers, citrate buffers, phosphate buffers, borate buffers and mixtures thereof. Specific buffer components useful in the present invention include boric acid, sodium borate, sodium phosphates, including mono, di- and tri-basic phosphates, such as sodium phosphate monobasic monohydrate and sodium phosphate dibasic heptahydrate, and mixtures thereof. It should be noted that any other suitable ophthalmically acceptable buffer components can be employed to maintain the pH of the ophthalmic formulation so that the ophthalmic formulation is provided with an acceptable pH, and the before-mentioned buffer components are merely examples of such buffer components.

When it is determined that the buffered ophthalmic formulation does not have the desired pH value, the pH of the aqueous buffered ophthalmic formulation can be

adjusted by the addition of an effective amount of either a base or an acid, as the case may be. Any suitable base or acid can be employed to adjust the pH of the aqueous buffered ophthalmic formulation which does not provide the ophthalmic formulation with toxic or deleterious properties which could harm either ophthalmic devices or the eye. An example of a base which can be used to adjust the pH of the aqueous buffered ophthalmic formulation is 1N sodium hydroxide; and an example of an acid which can be used to adjust the pH of the aqueous buffered ophthalmic formulation is 1N hydrochloric acid.

Further, in order to provide that the present ophthalmic formulations do not irritate the eye, e.g., the eye of the wearer of the contact lens treated using such formulations, it is important that the ophthalmic formulations have an osmolality (a measure of tonicity) of at least about 200 mOsmol/kg, preferably in the range of about 200 to about 350 or about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the formulation substantially corresponds to the tonicity of the fluids of the eye, in particular the human eye.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the ophthalmic formulation and do not have deleterious or toxic properties which could harm the eye. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The amount of ophthalmically acceptable tonicity component utilized can vary widely. In one embodiment, the tonicity component is preferably present in the ophthalmic formulation in an amount in the range of about 0.5 to about 0.9 weight/volume percent of the formulation.

Typical of ophthalmically acceptable inorganic salt tonicity components are alkali metal chlorides and alkaline earth metal chlorides, such as sodium chloride, potassium chloride, calcium chloride and magnesium chloride.

The formulations of the present invention include an ophthalmically acceptable medium, preferably an ophthalmically acceptable liquid aqueous medium. This medium often acts as a vehicle or carrier, e.g., as a solvent, for the other components in the formulation. A material is "ophthalmically acceptable" if the material can be placed into a mammalian eye without causing any substantial damage or harm to the eye. One particularly useful ophthalmically acceptable medium is water. Preferably, the medium, arid in fact the entire formulation, is sterile.

As previously set forth, the stabilized chlorine dioxide can also be utilized as a disinfecting agent in a disinfectant composition. When formulating such a disinfectant composition a suitable vehicle, such as sterilized water, is employed and at least about 0.02 weight-/volume percent stabilized chlorine dioxide is incorporated as the disinfecting agent. While the amount of stabilized chlorine dioxide employed as the disinfecting agent can vary widely, desirable results can be obtained when the stabilized chlorine dioxide utilized as the disinfecting agent is present in the disinfectant composition in an amount of from about 0.02 to 2.0 weight/volume percent, desirably from about 0.04 to about 0.1 weight-/volume percent, and more desirably from about 0.05 to about 0.08 weight/volume percent.

One or more additional components can be included in the present formulations based on the particular application for which the formulations are made. Thus, the present formulations can be made up as disinfecting compositions, cleaning compositions, wetting compositions, conditioning compositions, soaking compositions and the like. Also, the present formulations can be made up to be useful in performing two or more contact lens caring operations. For example, a disinfecting/cleaning formulation, or a cleaning/conditioning composition or even an all purpose lens care formulation can be made up and such multi-functional formulations are included within the scope of the present invention.

The additional component or components included in the present formulation are chosen to impart or provide at least one beneficial or desired property to the formulations. Such additional components may be selected from components which are conventionally used in one or more contact lens care compositions. Examples of such additional components include cleaning agents, wetting agents, nutrient agents, sequestering agents, viscosity builders, contact lens conditioning agents, antioxidants, and the like. These additional components are each included in the present formulations in an amount effective to impart or provide the beneficial or desired property to the compositions. For example, such additional components may be included in the present formulations in amounts similar to the amounts of such components used in other, e.g., conventional, contact lens care products.

Examples of useful wetting agents include polyvinyl alcohol, polyoxamers, polyvinyl pyrrollidone, hydroxypropyl methyl cellulose and mixtures thereof.

Examples of useful sequestering agents include disodium ethylene diamine tetraacetate, alkali metal hexametaphosphate, citric acid, sodium citrate and mixtures thereof.

Examples of useful viscosity builders include hydroxyethyl cellulose, hydroxymethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol and mixtures thereof.

Examples of useful antioxidants include sodium metabisulfite, sodium thiosulfate, N-acetylcysteine, butylated hydroxyanisole, butylated hydroxytoluene and mixtures thereof.

The present formulations may be used in the care of a contact lens, e.g., to disinfect the lens, to preserve the lens, to otherwise treat the lens and/or to make wearing the lens more safe and comfortable. The present formulations, made up appropriately by blending or combining the various components of the formulation together, may be used in conventional contact lens care regimens by using the present formulations, in place of prior conventional compositions. In many instances, these contact lens care regimens involve contacting the lens with the present formulation in an amount, and at conditions, effective to obtain the beneficial or desired contact lens care result.

For example, a contact lens to,be disinfected may be contacted with a disinfecting composition, e.g., aqueous solution, according to the present invention, preferably at a temperature in the range of about 0° C. to about 100° C., more preferably in the range of about 10° C. to about 60° C. and still more preferably in the range of about 15° C. to about 30° C. Contacting at or about ambient temperature is very convenient and useful. The contacting preferably occurs at or about atmospheric

pressure. The contacting preferably occurs for a time to substantially disinfect the lens being treated. Such contacting times can be in the range of about 1 minute to about 12 hours or more.

After this contacting, the disinfected contact lens can be taken from the composition and placed directly in an eye, e.g., a human eye, for safe and comfortable wear. Alternately, after being disinfected, the contact lens can be contacted with a second medium, e.g., a liquid aqueous medium such as a preserved isotonic saline solution in accordance with the present invention, prior to being placed in the eye of the wearer of the disinfected contact lens.

The contact lens care formulations disclosed herein are adaptable for use in most types of contact lens care equipment, such as ultrasonic cleaners and the like.

In order to more fully describe the present invention the following examples are set forth. However, the examples are merely illustrative in purpose and are not intended to be limiting upon the inventive concept as set forth in the appended claims.

EXAMPLE I

A series of experiments were performed to determine the antimicrobial properties of a borate buffered saline solution preserved with stabilized chlorine dioxide. The stabilized chlorine dioxide employed was the proprietary stabilized chlorine dioxide of Bio-Cide International, Inc. of Norman, Oklahoma, sold under the trademark Purogene. The concentration of the stabilized chlorine dioxide added to the borate buffered saline solution was varied.

The borate buffered saline solution had the following composition.

Ingredients	Percent (Weight/Volume)
Sodium Chloride USP	0.85
Boric Acid NF	0.10
Purified water USP*	To 100 ml

*Quantity sufficient (Q.S.) to provide 100 ml of solution.

The pH of the buffered solution was adjusted by the addition of either hydrochloric acid NF or sodium hydroxide NF so that the pH of the saline solution was within the range of about 7.7 to 7.9.

The stabilized chlorine dioxide was added to the borate buffered saline solution in the following concentrations:

Percent (weight/volume)
0.005
0.004
0.003
0.002

Each of the above concentrations of stabilized chlorine dioxide exhibited the desired preservative properties for the borate buffered saline solution. Further, all four concentrations of the stabilized chlorine dioxide exhibited good antimicrobial activity, with the three highest concentrations achieving total bacterial kill after 24 hours. Tests indicated that total kill of bacteria was achieved by the solution containing 0.002 weight-/volume percent stabilized chlorine dioxide after seven days.

EXAMPLE II

To compare the preservative efficacy of stabilized chlorine dioxide on a borate buffered ophthalmic solution, a preserving amount of stabilized chlorine dioxide having a raw material age of 54 months was utilized in one sample; and a similar preserving amount of stabilized chlorine dioxide having a raw material age of about 2 months was utilized in a second sample. Each of the samples of stabilized chlorine dioxide was the proprietary stabilized chlorine dioxide of Bio-Cide International, Inc. of Norman, Okla., sold under the trademark Purogene. No aging effect was detected between the two samples and their use as a preservative for borate buffered saline solutions. However, the aged stabilized chlorine dioxide (54 month age) possessed a slightly superior activity against the yeast *C. albicans.*

EXAMPLE III

A preservative efficacy test was performed on a borate buffered saline solution having a composition similar to that of Example I wherein 0.005 weight/volume percent stabilized chlorine dioxide was added to the borate buffered solution and the resulting mixture stored for 90 days at 45° C. At the end of the storage period, the sample was examined and it was determined that the stabilized chlorine dioxide was an effective preservative for a borate buffered saline solution.

EXAMPLE IV

An experiment was conducted to determine if a borate buffered saline solution containing 0.005 weight-/volume percent stabilized chlorine dioxide met the USP Efficacy criteria for ophthalmics as set forth in the U.S. Pharmacopeia (USP XXI, 1985). The stabilized chlorine dioxide employed was the proprietary stabilized chlorine dioxide of Bio-Cide International, Inc. of Norman, Okla., sold under the trademark Purogene. The criteria for preservatives requires that a 99.9% reduction of microbes challenge occur within 14 days of contact with the product being tested; and that no growth of yeast and fungi occur.

The borate buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide met the before-mentioned criteria for preservatives. However, a control solution of the borate buffered saline solution which did not contain the stabilized chlorine dioxide present did not meet this USP Efficacy criteria for ophthalmics.

EXAMPLE V

A 21 day subacute eye toxicity study in rabbits was conducted using a borate buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide. The stabilized chlorine dioxide was as identified in Example I. The borate buffered saline solution containing the stabilized chlorine dioxide had the following composition:

Ingredients	Percent (weight/volume)
Stabilized Chlorine Dioxide	0.005
Sodium Chloride USP	0.85
Boric Acid NF	0.10
Purified Water USP*	To 100 ml

*Quantity sufficient (Q.S.) to provide 100 ml solution.

The pH of the above buffered saline solution was adjusted so that the pH of the solution was between 7.7 and 7.9.

The ocular effects of the buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide were evaluated in rabbit eyes in conjunction with Permalens soft contact lenses. Test eye lenses were subjected to daily cleaning, rinsing, and overnight soaking with the borate buffered saline solution containing stabilized chlorine dioxide. Control eye lenses were subjected to the same regimen using preserved normal saline solution. Lenses were fit directly to the eye and worn daily for a minimum of 8 hours for 21 consecutive days.

Eyes were observed daily for discomfort at lens insertion and for gross ocular reactions at lens removal. Slit lamp biomicroscopy was performed weekly. Pachometry and rose bengal staining were performed at the conclusion of the experiment. Histopathological evaluation was performed on eyes from three animals. No significant ocular reactions were noted.

The following is a summation of the results of the experiments set forth above:

A. Discomfort: No ocular discomfort was noted at lens insertion throughout the study.

B. Gross Observations: At the time of lens removal, +1 hyperemia was noted in one control eye on Day 17. No other ocular reactions were noted.

C. Slit Lamp Examinations (Days 7, 14 and 21): No ocular reactions were noted in any rabbit.

D. Corneal Metabolism (Days 7, 14 and 21).: No test related changes in corneal metabolism, as measured by corneal thickness, were noted throughout the study.

E. Cytotoxicity (Day 21): Rose bengal staining appeared normal in both eyes of all rabbits, indicating that corneal epithelial cell vitality was not affected by the solution tested.

F. Histopathological Evaluation: No microscopic changes which can be specifically related to the test regimen were apparent among the eyes and extraocular tissues examined. There were no predictable microscopic differences observed when comparing the test eyes and extraocular tissues with the control eyes and extraocular tissues.

The above data indicates that a borate buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide, in conjunction with Permalens soft contact lenses, is not discomforting, irritating, toxic or cytotoxic to rabbit eyes following 21 consecutive days of testing.

EXAMPLE VI

A 1 day acute eye toxicity and cytotoxicity study in rabbits was conducted using a borate buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide. The stabilized chlorine dioxide was as identified in Example I. The borate buffered saline solution containing the stabilized chlorine dioxide had the following composition:

Ingredients	Percent (weight/volume)
Stabilized Chlorine Dioxide	0.005
Sodium Chloride USP	0.85
Boric Acid NF	0.10
Purified Water USP*	To 100 ml

*Quantity Sufficient (Q.S.) to provide 100 ml solution.

The pH of the above buffered saline solution was adjusted so that the pH of the solution was between 7.7 and 7.9.

The ocular effects of the buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide were evaluated in rabbit eyes in conjunction with Permalens soft contact lenses and multiple topical instillations. Test eye lenses were subjected to overnight soaking in the borate buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide followed by direct fit to the eye and 8 hours of wear with topical instillations of the test solution performed at a rate of one drop every one-half hour. Eyes were observed for discomfort and/or gross ocular reactions at lens fit, at each instillation and at lens removal. Slip lamp biomicroscopy was performed following lens removal. Control eyes were subjected to the same regimen using preserved normal saline.

The following is a summation of the results of the experiments set forth above:

A. Discomfort: No ocular discomfort was noted at lens fit or at any instillation period throughout the study.

B. Gross Observations: No ocular reactions were noted at any instillation period or at lens removal.

C. Slip Lamp Examinations: No ocular reactions were noted in any rabbit.

D. Cytotoxicity Rose bengal staining appeared normal in both eyes of all rabbits, indicating that epithelia cell vitality was not affected by the solutions tested.

The above data indicates that a borate buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide, in conjunction with Permalens soft contact lenses, is not discomforting, irritating, toxic or cytotoxic to rabbit eyes following this exaggerated method of testing.

EXAMPLE VII

An acute eye toxicity and cytotoxicity study in rabbits was conducted using a borate buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide. The stabilized chlorine dioxide was that identified in Example I. The borate buffered saline solution containing the stabilized chlorine dioxide had the following composition:

Ingredients	Percent (weight/volume)
Stabilized Chlorine Dioxide	0.005
Sodium Chloride USP	0.85
Boric Acid NF	0.10
Purified water USP*	To 100 ml

*Quantity Sufficient (Q.S.) to provide 100 ml solution.

The pH of the above buffered saline solution was adjusted so that the pH of the solution was between 7.7 and 7.9.

The ocular effects of the buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide were evaluated in rabbit eyes following 1 day of multiple topical instillations performed at a

rate of one drop every one-half hour for 8 hours. Test eyes were treated with the borate buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide and control eyes were treated with a preserved normal saline solution.

Eyes were observed for discomfort and/or gross ocular reactions at each instillation. Slit lamp biomicroscopy was performed following the last instillation period. No ocular reactions were noted in the test eyes.

The following is a summation of the results of the experiments set forth above:

A. Discomfort: +1 discomfort, lasting up to 30 seconds, was noted in the control eye at 3 of 48 instillations involving two of three rabbits.

B. Gross Observations: No ocular reactions were noted at any instillation period.

C. Slit Lamp Examinations: No ocular reactions were noted in any rabbit.

D. Cytotoxicity: Rose bengal staining appeared normal in both eyes of all rabbits, indicating that epithelial cell vitality was not affected by the preparations tested.

The above data indicates that a borate buffered saline solution containing 0.005 weight/volume percent stabilized chlorine dioxide is not discomforting, irritating, toxic or cytotoxic to rabbit eyes following this exaggerated method of testing.

EXAMPLE VIII (COMPARATIVE)

A series of compositions were prepared using sterilized distilled water and varying concentrations of the proprietary stabilized chlorine dioxide sold by Bio-Cide International, Inc. of Norman, Okla., under the trademark Purogene.

Each of these compositions was tested to determine its pH and osmolality. After the compositions were prepared, they were allowed to equilibrate overnight before the pH and osmolality were determined.

Results of these tests were as follows:

Concentration of Stabilized Chlorine Dioxide, (w/v) %	pH	Osmolality, mOsmol/kg
0.005	6.4	5
0.02	6.8	13
0.1	8.6	55
0.2	9.0	105

These results indicate that simple solutions of stabilized chlorine dioxide in sterilized water have varying pHs, which are often outside the range of about 6.8 to about of the present compositions. Also, such simple solutions have tonicity values or osmolalities substantially outside the range of at least about 200 mOsmol/kg of the present compositions. Put another way, such simple aqueous stabilized chlorine solutions are not effective to provide preserved compositions which are ophthalmically acceptable or compatible with the eye so as to be used without eye discomfort or irritation.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

What is claimed is:

1. A method for preserving an aqueous ophthalmic formulation so as to enhance the shelf life thereof comprising incorporating into said aqueous ophthalmic formulation stabilized chlorine dioxide in an amount effective to act as the sole preservative in said aqueous ophthalmic formulation, at least one ophthalmically acceptable buffer component in an amount effective to maintain said aqueous ophthalmic formulation at a pH in the range of about 6.8 to about 8, and at least one ophthalmically acceptable tonicity component in an amount effective to maintain said aqueous ophthalmic formulation at an osmolality of at least about 200 mOsmol/kg, provided that said aqueous ophthalmic formulation is ophthalmically acceptable and no germicidally effective amounts of any positively charged, nitrogen-containing cationic polymers are incorporated into said aqueous ophthalmic formulation.

2. The method of claim **1** wherein said stabilized chlorine dioxide is present in said aqueous ophthalmic formulation in an amount in the range of about 0.0002 to about 0.02 weight/volume percent.

3. The method of claim **1** wherein said stabilized chlorine dioxide is present in said aqueous ophthalmic formulation in an amount in the range of about 0.004 to about 0.01 weight/volume percent.

4. The method of claim **1** wherein said at least one ophthalmically acceptable buffer component is present in an amount effective to maintain said aqueous ophthalmic formulation at a pH in the range of about 7 to about 7.5.

5. The method of claim **1** wherein said at least one ophthalmically acceptable tonicity component is present in an amount effective to maintain said aqueous ophthalmic formulation at an osmolality in the range of about 200 to about 400 mOsmol/kg.

6. The method of claim **1** wherein said aqueous ophthalmic formulation is a solution.

7. A method for preserving an aqueous ophthalmic solution so as to enhance the shelf life thereof comprising incorporating into said aqueous ophthalmic solution stabilized chlorine dioxide in an amount effective to act as the sole preservative in said aqueous ophthalmic solution in the range of about 0.002 to about 0.02 weight/volume percent, at least one ophthalmically acceptable buffer component in an amount effective to maintain said aqueous ophthalmic solution at a pH in the range of about 6.8 to about 8, and at least one ophthalmically acceptable tonicity component in an amount effective to maintain said aqueous ophthalmic solution at an osmolality in the range of about 200 to about 400 mOsmol/kg, provided that said aqueous ophthalmic solution is ophthalmically acceptable and substantially no germicidally effective amounts of any positively charged, nitrogen-containing cationic polymers are incorporated into said aqueous ophthalmic solution.

8. A preserved ophthalmic formulation comprising an ophthalmically acceptable aqueous medium and, included therein, stabilized chlorine dioxide in an amount effective to act as the sole preservative in said ophthalmically acceptable aqueous medium, at least one ophthalmically acceptable buffer component in an amount effective to maintain said ophthalmically acceptable aqueous medium at a pH in the range of about 6.8 to about 8, and at least one ophthalmically acceptable tonicity component in an amount effective to maintain said ophthalmically acceptable aqueous medium at an osmolality of at least about 200 mOsmol/kg, provided that said preserved ophthalmic formulation is ophthalmically acceptable and is free of germicidally effective

amounts of any positively charged, nitrogen-containing cationic polymers.

9. The preserved ophthalmic formulation of claim **8** wherein said stabilized chlorine dioxide is present in said preserved ophthalmic formulation in an amount in the range of about 0.0002 to about 0.02 weight/volume percent.

10. The preserved ophthalmic formulation of claim **8** wherein said stabilized chlorine dioxide is present in said preserved ophthalmic formulation in an amount in the range of about 0.004 to about 0.01 weight/volume percent.

11. The preserved ophthalmic formulation of claim **8** wherein said at least one ophthalmically acceptable tonicity component is selected from the group consisting of alkali metal chlorides and alkaline earth metal chlorides and mixtures thereof.

12. The preserved ophthalmic formulation of claim **8** wherein said at least one ophthalmically acceptable tonicity component comprises sodium chloride.

13. The preserved ophthalmic formulation of claim **8** wherein said at least one ophthalmically acceptable tonicity component comprises an alkaline earth metal salt selected from the group consisting of calcium chloride and magnesium chloride and mixtures thereof.

14. The preserved ophthalmic formulation of claim **8** wherein said at least one buffer component is selected from the group consisting of potassium phosphates, boric acid, sodium borate, sodium phosphates and mixtures thereof.

15. The preserved ophthalmic formulation of claim **8** wherein said at least one ophthalmically acceptable buffer component is present in an amount effective to maintain said ophthalmically acceptable aqueous medium at a pH in the range of about 7 to about 7.5.

16. The preserved ophthalmic formulation of claim **8** wherein said at least one ophthalmically acceptable tonicity component is present in an amount effective to maintain said ophthalmically acceptable aqueous medium at an osmolality in the range of about 200 to about 400 mOsmol/kg.

17. The preserved ophthalmic formulation of claim **8** which is a solution.

18. A preserved ophthalmic solution comprising an ophthalmically acceptable aqueous solution and, included therein, stabilized chlorine dioxide in an amount effective to act as the sole preservative in said ophthalmically aqueous acceptable solution in the range of about 0.002 to about 0.02 weight/volume percent, at least one ophthalmically acceptable buffer component in an amount effective to maintain said ophthalmically acceptable aqueous solution at a pH in the range of about 6.8 to about 8, and at least one ophthalmically acceptable tonicity component in an amount effective to maintain said ophthalmically acceptable aqueous solution at an osmolality in the range of about 200 to about 400 mOsmol/kg, provided that said preserved ophthalmic solution is ophthalmically acceptable and is free of germicidally effective amounts of any positively charged, nitrogen-containing polymers.

* * * * *

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(12) **United States Patent**
Olejnik et al.

(10) **Patent No.: US 6,627,210 B2**
(45) **Date of Patent: *Sep. 30, 2003**

(54) **COMPOSITIONS CONTAINING α-2-ADRENERGIC AGONIST COMPONENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 8 days.

This patent is subject to a terminal disclaimer.

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(22) Filed: **Jul. 10, 2001**

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(52) **U.S. Cl.** **424/427**; 424/400; 424/401; 424/466; 424/422; 514/772.4; 514/772.6

(58) **Field of Search** 424/427, 400, 424/422, 661, 407; 514/772.4, 772.6

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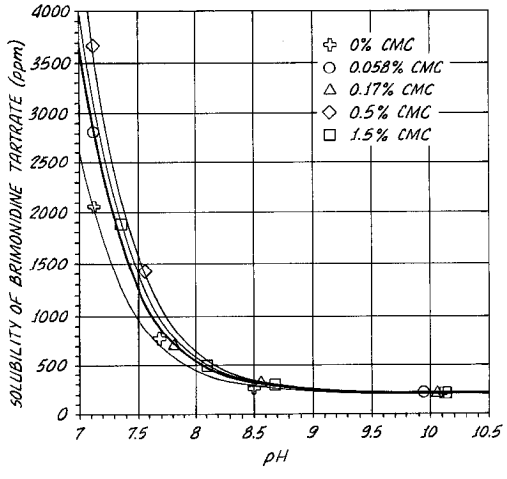
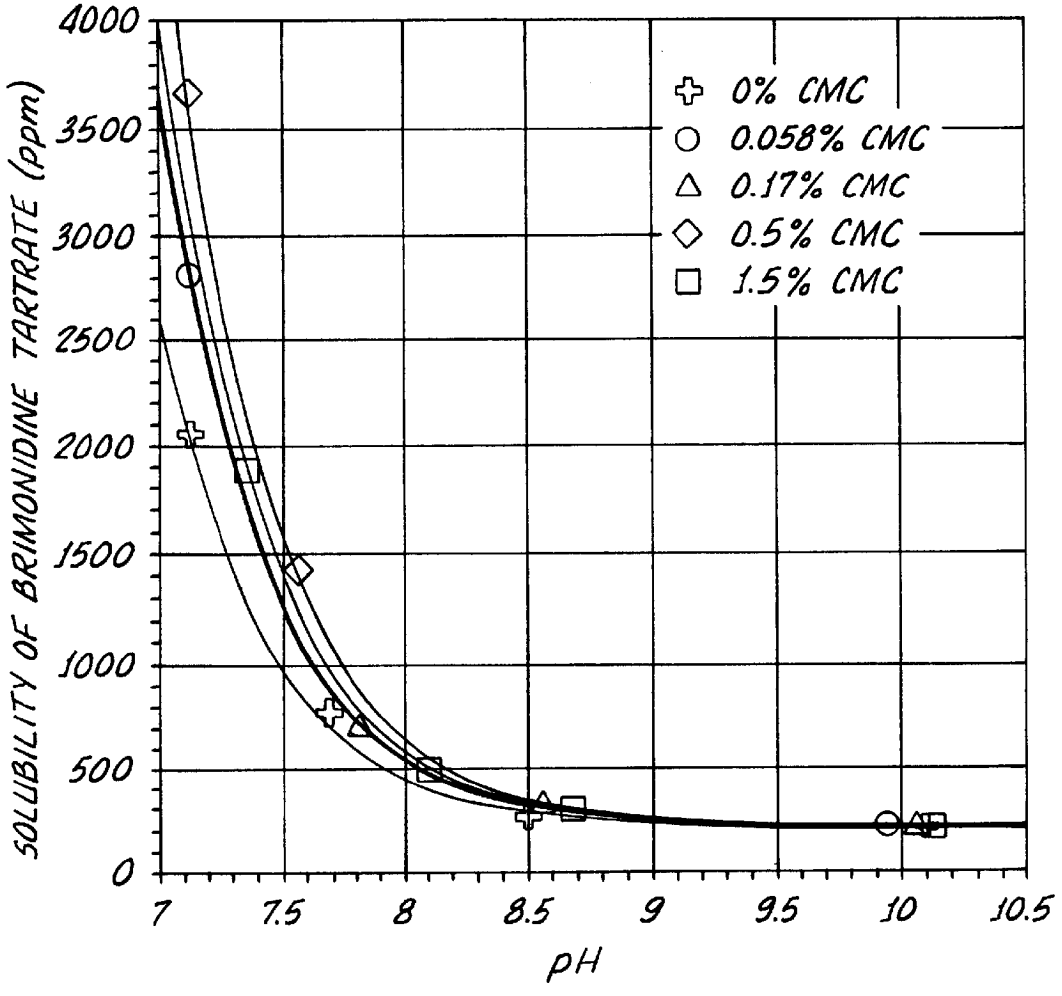
(57) **ABSTRACT**

Compositions useful for improving effectiveness of alpha-2-adrenergic agonist components include carrier components, alpha-2-adrenergic agonist components, solubility enhancing components which aid in solubilizing the alpha-2-adrenergic agonist components. In one embodiment, the alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. In another embodiment, the solubility enhancing components include carboxymethylcellulose.

34 Claims, 1 Drawing Sheet




SOLUBILITY OF BRIMONIDINE TARTRATE (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0
7
7.5
8
8.5
9
9.5
10
10.5
pH
0% CMC
0.058% CMC
0.17% CMC
0.5% CMC
1.5% CMC

COMPOSITIONS CONTAINING α-2-ADRENERGIC AGONIST COMPONENTS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application 60/218,200 filed Jul. 14, 2000.

BACKGROUND OF THE INVENTION

The present invention relates to compositions containing alpha-2-adrenergic agonist components. More particularly, the invention relates to such compositions in which the alpha-2-adrenergic agonist components have enhanced solubility at the therapeutically effective concentrations.

Alpha-2-adrenergic agonist components include chemical entities, such as compounds, ions, complexes and the like, which are effective to act on or bind to Alpha-2-adrenergic receptors and provide a therapeutic effect. Alpha-2-adrenergic agonist components means the agonists themselves and any and all precursors thereof, metabolites thereof and combinations thereof. One of the continuing challenges of formulating compositions having alpha-2-adrenergic agonist components is to render such components more effective. For example, alpha-2-adrenergic agonist components in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration.

Additionally, the dispensed or administered alpha-2-adrenergic agonist components should advantageously be soluble in biological systems or environments, for example, for effective or enhanced in vivo diffusion through cell membranes or lipid bilayers. Some alpha-2-adrenergic agonist components with higher pKa's, for example, greater than about 7, tend to diffuse very well through lipid membranes at pH valves near their pka, because in such circumstances they are predominantly unionized in neutral to alkaline biological environments. However, some of these alpha-2-adrenergic agonist components become insoluble at neutral to alkaline biological pH's. Such insolubility may decrease membrane diffusion capabilities, rendering the alpha-2-adrenergic agonist components less effective and/or their therapeutic effects more variable at a given dosage. Furthermore, solubilized alpha-2-adrenergic agonist components provide other benefits, for example, reduced irritation to tissues that interact with alpha-2-adrenergic agonist components.

There continues to be a need for new compositions containing alpha-2-adrenergic agonist components.

SUMMARY OF THE INVENTION

New alpha-2-adrenergic agonist component-containing compositions have been discovered. The present compositions contain certain materials which are effective in at least aiding or assisting in solubilizing the alpha-2-adrenergic agonist components in the compositions, and preferably in environments to which the compositions are administered or introduced, for example, biological environments, such as the human eye. Preferably, solubilization of the alpha-2-adrenergic agonist components in accordance with the present invention facilitates transport of such components across lipid membranes. Also, preferably such solubilization allows the provision of more reliable and reproducible dosage forms of the drug. In addition, alpha-2-adrenergic agonist component-containing compositions have been discovered which include preservatives which provide substantial advantages, for example, reduced adverse interactions with the alpha-2-adrenergic agonist components and/or with the patients to whom the compositions are administered, while maintaining preservative effectiveness.

The present compositions preferably enhance the effectiveness of alpha-2-adrenergic agonist components by increasing the apparent water solubility of the alpha-2-adrenergic agonist components, preferably at pH's higher than neutral. The present compositions include, in addition to the adrenergic agonist components, solubility enhancing components (SECs) in amounts effective to enhance the solubility of the alpha-2-adrenergic agonist components. Preferably, the alpha-2-adrenergic agonist components are more soluble in the present compositions having, for example, pH's of about 7 or greater, relative to similar compositions without the SECs. In another embodiment, the alpha-2-adrenergic agonist components of the present compositions are more soluble in neutral, preferably alkaline, biological environments into which the compositions are administered relative to alpha-2-adrenergic agonist components in similar compositions without the SECs.

In one embodiment, the alpha-2-adrenergic agonist components include imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. Preferably, the alpha-2-adrenergic agonist components include quinoxaline components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and biologically compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is referred to as "Brimonidine tartrate."

In a preferred embodiment, the alpha-2-adrenergic agonist components, such as those listed above, are specific for the alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and/or alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonist components are unionized in the compositions. Preferably, the alpha-2-adrenergic agonist components are also unionized in the biological environment into which the compositions are administered.

In a useful embodiment, the SEC includes a polyanionic component. As used herein, the term "polyanionic component" refers to a chemical entity, for example, an ionically charged species, such as an ionically charged polymeric material, which includes more than one discrete anionic charge, that is multiple discrete anionic charges. Preferably, the polyanionic component is selected from polymeric materials having multiple anionic charges, and mixtures thereof.

Particularly useful polyanionic components are selected from anionic polymers derived from acrylic acid (meaning to include polymers from acrylic acid, acrylates and the like and mixtures thereof), anionic polymers derived from methacrylic acid (meaning to include polymers from methacrylic acid, methacrylates, and the like and mixtures thereof), anionic polymers derived from alginic acid (meaning to include alginic acid, alginates, and the like and mixtures thereof), anionic polymers of amino acids (meaning to include polymers of amino acids, amino acid salts, and the like and mixtures thereof), and the like, and mixtures

thereof. Very useful polyanionic components are those selected from anionic cellulose derivatives and mixtures thereof, especially carboxymethylcelluloses.

The polyanionic component preferably is sufficiently anionic to interact with or otherwise affect, in particular increase, the solubility of the alpha-2-adrenergic components. This interaction preferably is sufficient to render the alpha-2-adrenergic components substantially completely soluble at therapeutically effective concentrations. The amount of SEC in the composition preferably is in the range of about 0.1% (w/v) to about 30% (w/v), more preferably about 0.2% (w/v) to about 10% (w/v), and even more preferably about 0.2% (w/v) to about 0.6% (w/v).

The compositions include carrier components, for example, aqueous liquid carrier components. In one embodiment, the compositions have pH's of about 7 or greater, preferably about 7 to about 9, and are ophthalmically acceptable.

In a preferred embodiment, a composition is provided which includes an alpha-2-adrenergic agonist component in an amount effective to provide at least one therapeutic benefit to a patient to whom the composition is administered, an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component and an aqueous liquid carrier component. The alpha-2-adrenergic agonist component preferably comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. The anionic cellulose derivative preferably comprises a carboxymethylcellulose. The concentration of the anionic cellulose derivative in the composition should be about 0.2% (w/v) to about 0.6% (w/v).

In a preferred embodiment, the present compositions are ophthalmically acceptable, e.g. the compositions do not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered.

In one broad aspect of the invention, complexes are formed in the compositions. In one embodiment, the complexes include monomer units derived from at least one quinoxaline component. In a preferred embodiment, the complexes of the present invention are dimers. In a particularly preferred embodiment, the complexes are complexes, especially dimers, of Bromodidine tartrate.

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component and a preservative component in an effective amount to at least aid in preserving the compositions. Preferably, the preservative components include oxychloro components, such as compounds, ions, complexes and the like which are biologically acceptable, chemically stable and do not substantially or significantly detrimentally affect the an alpha-2-adrenergic agonist component in the compositions or the patients to whom the compositions are administered. Such compositions preferably are substantially free of cyclodextrins in the compositions or the patients to whom the compositions are administered.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art.

Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** is a graph of soluble Brimonidine tartrate verses pH at various carboxymethylcellulose concentrations.

DETAILED DESCRIPTION OF THE INVENTION

Compositions comprising alpha-2-adrenergic agonist components and SECs are provided. The alpha-2-adrenergic agonist components in the present compositions are made more soluble and may be more effectively utilized as therapeutic agents. The SECs employed in the present compositions may be effective in the solubilization of ionized alpha-2-adrenergic agonist components, unionized alpha-2-adrenergic agonist components or both. The present compositions include liquid carrier components and have the characteristics of liquid, for example, aqueous liquid, solutions.

Preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's greater than 7, as compared to identical alpha-2-adrenergic agonist components, at comparable concentrations, in similar compositions without the SECs. More preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's in the range of about 7 to about 10 and, as compared to identical alpha-2-adrenergic agonist components in similar compositions, at comparable concentrations, without the SECs.

Without wishing to be limited by any theory or mechanism of operation, it is believed that solubilized alpha-2-adrenergic agonist components are better able to cross the lipid membranes relative to unsolubilized alpha-2-adrenergic agonist components. It is further believed that the solubilized alpha-2-adrenergic agonist components are physically smaller and are therefore more able to physically permeate or diffuse through the lipid membranes.

In one embodiment, the SECs of this invention are capable of solubilizing the alpha-2-adrenergic agonist components in the biological environments into which they are introduced at therapeutically effective concentrations. Preferably, the biological environments into which the present compositions are introduced have pH's ranging from about 7 to about 9. For example, a composition comprising a SEC and an alpha-2-adrenergic agonist component may be administered to the cornea of an eye, which has a pH of about 7, wherein the alpha-2-adrenergic agonist component is substantially solubilized at the administered area. Furthermore, in one embodiment, the alpha-2-adrenergic agonist components solubilized by SECs at the administered area diffuse through biological lipid membranes more readily than alpha-2-adrenergic agonist components which are not solubilized by SECs. The solubilization of alpha-2-adrenergic agonist components preferably reduces irritation to sensitive tissues in contact or interacting with the alpha-2-adrenergic agonist components.

The presently useful alpha-2-adrenergic agonist components preferably are chosen to benefit from the presence of the SECs. In general, the alpha-2-adrenergic agonist components are provided with increased apparent solubility, preferably increased apparent water solubility, by the presence of the SECs.

Examples of alpha-2-adrenergic agonist components include molecules containing amines. Preferably, the alpha-2-adrenergic agonist components are amine-containing molecules with pKa's of greater than about 7, more preferably about 7 to about 9.

Alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. As used herein, the term alpha-2 adrenergic agonist includes chemical entities, such as compounds, ions, complexes and the like, that produce a net sympatholytic response, resulting in increased

accommodation, for example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or for example, to postsynaptic alpha-2 receptors on smooth muscle cells. A sympatholytic response is characterized by the inhibition, diminishment, or prevention of the effects of impulses conveyed by the sympathetic nervous system. The alpha-2 adrenergic agonists of the invention bind to the alpha-2 adrenergic receptors presynaptically, causing negative feedback to decrease the release of neuronal norepinephrine. Additionally, they also work on alpha-2 adrenergic receptors postsynaptically, inhibiting beta-adrenergic receptor-stimulated formation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2 adrenergic receptors on other intracellular pathways. Activity at either pre- or postsynaptic alpha-2 adrenergic receptors will result in a decreased adrenergic influence. Decreased adrenergic influence results in increased contraction resulting from cholinergic innervations. Alpha-2 adrenergic agonists also include compounds that have neuroprotective activity. For example, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is an alpha-2-adrenergic agonist which has a neuroprotective activity through an unknown mechanism.

Without limiting the invention to the specific groups and compounds listed, the following is a list of representative alpha-2 adrenergic agonists useful in this invention: iminoimidazolines, including clonidine, apraclonidine; imidazolines, including naphazoline, xymetazoline, tetrahydrozoline, and tramazoline; imidazoles, including detomidine, medetomidine, and dexmedetomidine; azepines, including B-HT 920 (6-allyl-2-amino-5,6,7,8 tetrahydro-4H-thiazolo[4,5-d]-azepine and B-HT 933; thiazines, including xylazine; oxazolines, including rilmenidine; guanidines, including guanabenz and guanfacine; catecholamines; and the like and derivatives thereof.

Particularly useful alpha-2-adrenergic agonists include quinoxaline components. In one embodiment, the quinoxaline components include quinoxaline, derivatives thereof and mixtures thereof. Preferably, the derivatives of quinoxaline include (2-imidozolin-2-ylamino) quinoxaline. More preferably, the derivatives of quinoxaline include 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline. The "halide" of the 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline may be a fluorine, a chlorine, an iodine, or preferably, a bromine, to form 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Even more preferably, the derivatives of quinoxaline to be used in accordance with this invention include a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, or Brimonidine tartrate.

Other useful quinoxaline derivatives are well known. For example, useful derivatives of a quinoxaline include the ones disclose by Burke et al U.S. Pat. No. 5,703,077. See also Danielwicz et al U.S. Pat. No. 3,890,319. Each of the disclosures of Burke et al and Danielwicz et al is incorporated in its entirety by reference herein.

The quinoxaline and derivatives thereof, for example Brimonidine tartrate, are amine-containing and preferably have pKa's of greater than 7, preferably about 7.5 to 9.

Analogs of the foregoing compounds that function as alpha-2 adrenergic agonists also are specifically intended to be embraced by the invention.

Preferably, the alpha-2-adrenergic agonists, for example the ones listed above, are effective toward activating alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonists, for example Brimonidine tartrate, are substantially unionized in the compositions. In another embodiment, the adrenergic compounds are substantially unionized in the environment to which they are administered, for example the cornea. Without wishing to be limited by any theory or mechanism of action, it is believed that the unionized forms of the adrenergic compounds facilitate their permeation across membrane lipid bilayers.

Any suitable SEC may be employed in accordance with the present invention. In one embodiment, the SECs include pyrrolinidone components. Examples of pyrrolinidone components are polyvinylpyrrolinidones and derivatives thereof. In a preferred embodiment, the SECs include polyanionic components. The useful polyanionic components include, but are not limited to, those materials which are effective in increasing the apparent solubility, preferably water solubility, of poorly soluble alpha-2-adrenergic agonist components and/or enhance the stability of the alpha-2-adrenergic agonist components and/or reduce unwanted side effects of the alpha-2-adrenergic agonist components. Furthermore, the polyanionic component is preferably ophthalmically acceptable at the concentrations used. Additionally, the polyanionic component preferably includes three (3) or more anionic (or negative) charges. In the event that the polyanionic component is a polymeric material, it is preferred that each of the repeating units of the polymeric material include a discrete anionic charge. Particularly useful anionic components are those which are water soluble, for example, soluble at the concentrations used in the presently useful liquid aqueous media, such as a liquid aqueous medium containing the alpha-2-adrenergic components.

The polyanionic component is preferably sufficiently anionic to interact with the alpha-2-adrenergic agonist component. Such interaction is believed to be desirable to solubilize the alpha-2-adrenergic agonist component and/or to maintain such alpha-2-adrenergic agonist component soluble in the carrier component, for example a liquid medium.

Polyanionic components also include one or more polymeric materials having multiple anionic charges. Examples include:

- metal carboxymethylstarchs
- metal carboxymethylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles heparin
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - metal acrylates and methacrylates
  - alginic acid
  - metal alginates
  - vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - p-styrenesulfonic acid
  - metal p-styrenesulfonate
  - 2-methacryloyloxyethylsulfonic acids
  - metal 2-methacryloyloxethylsulfonates
  - 3-methacryloyloxy-2-hydroxypropylsulonic acids
  - metal 3-methacryloyloxy-2-hydroxypropylsulfonates
  - 2-acrylamido-2-methylpropanesulfonic acids
  - metal 2-acrylamido-2-methylpropanesulfonates
  - allylsulfonic acid
  - metal allylsulfonate and the like.

In another embodiment, the polyanionic components include anionic polysaccharides which tend to exist in

ionized forms at higher pH's, for example, pH's of about 7 or higher. The following are some examples of anionic polysaccharides which may be employed in accordance with this invention.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose.

Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks.

Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of which can be sulfated or nonsulfated, joined by alternating 1–3 and beta 1–4 glycosidic linkages. Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss.

Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water.

Other anionic polysaccharides found useful in the present invention are hydrophilic colloidal materials and include the natural gums such as gellan gum, alginate gums, i.e., the ammonium and alkali metal salts of alginic acid and mixtures thereof. In addition, chitosan, which is the common name for deacetylated chitin is useful. Chitin is a natural product comprising poly-(N-acetyl-D-glucosamine). Gellan gum is produced from the fermentation of pseudomonas elodea to yield an extracellular heteropolysaccharide. The alginates and chitosan are available as dry powders from Protan, Inc., Commack, N.Y. Gellan gum is available from the Kelco Division of Merk & Co., Inc., San Diego, Calif.

Generally, the alginates can be any of the water-soluble alginates including the alkali metal alginates, such as sodium, potassium, lithium, rubidium and cesium salts of alginic acid, as well as the ammonium salt, and the soluble alginates of an organic base such as mono-, di-, or triethanolamine alginates, aniline alginates, and the like. Generally, about 0.2% to about 1% by weight and, preferably, about 0.5% to about 3.0% by weight of gellan, alginate or chitosan ionic polysaccharides, based upon the total weight of the composition, are used to obtain the gel compositions of the invention.

Preferably, the anionic polysaccharides are cyclized. More preferably, the cyclized anionic polysaccharides include less than ten monomer units. Even more preferably, the cyclized polysaccharides include less than six monomer units.

In one embodiment, a particularly useful group of cyclized anionic polysaccharides includes the cyclodextrins. Examples of the cyclodextrin group include, but are not limited to: α-cyclodextrin, derivatives of α-cyclodextrin, β-cyclodextrin, derivatives of β-cyclodextrin, γ-cyclodextrin, derivatives of γ-cyclodextrin, carboxymethyl-β-cyclodextrin, carboxymethyl-ethyl-β-cyclodextrin, diethyl-β-cyclodextrin, dimethyl-β-cyclodextrin, methyl-β-cyclodextrin, random methyl-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and the like and mixtures thereof. Sulfobutylether-β-cyclodextrin is a preferred cyclized anionic polyasaccharide in accordance with the present invention. It is advantageous that the SEC's, including the above mentioned cyclodextrins, employed in this invention be, at the concentration employed, non-toxic to the mammal, human, to inhibit the present incorporation is administered. As used herein, the term "derivatives" as it relates to a cyclodextrin means any substituted or otherwise modified compound which has the characteristic chemical structure of a cyclodextrin sufficiently to function as a cyclodextrin component, for example, to enhance the solubility and/or stability of active components and/or reduce unwanted side effects of the active components and/or to form inclusive complexes with active components, as described herein.

Although cyclodextrins and/or their derivatives may be employed as SECs, one embodiment of the invention may include SECs other than cyclodextrins and/or their derivatives.

A particularly useful and preferred class of polyanionic component includes anionic cellulose derivatives. Anionic cellulose derivatives include metal carboxymethylcelluloses, metal carboxymethylhydroxyethylcelluloses and hydroxypropylmethylcelluloses and derivatives thereof.

The present polyanionic components often can exist in the unionized state, for example, in the solid state, in combination with a companion or counter ion, in particular a plurality of discrete cations equal in number to the number of discrete anionic charges so that the unionized polyanionic component is electrically neutral. For example, the present unionized polyanionic components may be present in the acid form and/or in combination with one or more metals. Since the polyanionic components are preferably ophthalmically acceptable, it is preferred that the metal associated with the unionized polyanionic component be ophthalmically acceptable in the concentrations used. Particularly useful metals include the alkali metals, for example, sodium and potassium, the alkaline earth metals, for example, calcium and magnesium, and mixtures thereof. Sodium is very useful to provide the counter ion in the unionized polyanionic component. Polyanionic components which, in the unionized states, are combined with cations other than H^+ and metal cations can be employed in the present invention.

The amount of SEC in the present compositions is not of critical importance so long as solubility at the alpha-2-adrenergic agonist component is at least somewhat increased and is present in a biologically acceptable amount. Such amount should be effective to perform the desired function or functions in the present composition and/or after administration to the human or animal. In one embodiment, the amount of SEC, preferably the polyanionic component, is sufficient to complex at least in a major amount, and more preferably substantially all, of the alpha-2-adrenergic agonist component in the present composition. In one useful embodiment, the amount of polyanionic component in the present composition is in the range of about 0.1% to about 30% (w/v) or more of the composition. Preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 10% (w/v). More preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 0.6% (w/v). Even more preferably, the polyanionic component is carboxymethylcellulose and is present in the composition in the range of about 0.2% (w/v) to about 0.6% (w/v). A particularly useful concentration of carboxymethylcellulose in the present compositions is about 0.5%.

In one embodiment, the SECs, for example a carboxymethylcellulose, assist in solubilizing the alpha-2-adrenergic agonist components in the compositions. Although the SECs are capable aiding in the solubilization of ionized alpha-2-adrenergic agonist components, it is

preferable that the SECs used in this invention could assist in the solubilization of unionized alpha-2-adrenergic agonist components. For example, in one embodiment, carboxymethylcellulose may help solubilize ionized alpha-2-adrenergic agonist components. In another embodiment, carboxymethylcellulose may help solubilize unionized alpha-2-adrenergic agonist components. In a preferred embodiment, the carboxylmethylcellulose helps solubilize ionized Brimonidine tartrate in the compositions. More preferably, the carboxylmethylcellulose helps solubilize unionized Brimonidine tartrate in the compositions.

In one embodiment, the compositions may also include preservative components or components which assist in the preservation of the composition. The preservative components selected so as to be effective and efficacious as preservatives in the present compositions, that is in the presence of polyanionic components, and preferably have reduced toxicity and more preferably substantially no toxicity when the compositions are administered to a human or animal.

Preservatives or components which assist in the preservation of the composition which are commonly used in pharmaceutical compositions are often less effective when used in the presence of solubilizing agents. In certain instances, this reduced preservative efficacy can be compensated for by using increased amounts of the preservative. However, where sensitive or delicate body tissue is involved, this approach may not be available since the preservative itself may cause some adverse reaction or sensitivity in the human or animal, to whom the composition is administered.

Preferably, the present preservative components or components which assist in the preservation of the composition, preferably the alpha-2-adrenergic agonist components therein, are effective in concentrations of less than about 1% (w/v) or about 0.8% (w/v) and may be 500 ppm (w/v) or less, for example, in the range of about 10 ppm(w/v) or less to about 200 ppm(w/v). Preservative components in accordance with the present invention preferably include, but are not limited to, those which form complexes with the polyanionic component to a lesser extent than does benzalkonium chloride.

Very useful examples of the present preservative components include, but are not limited to oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof. Specific examples of oxy-chloro components useful as preservatives in accordance with the present invention include hypochlorite components, for example hypochlorites; chlorate components, for example chlorates; perchlorate components, for example perchlorates; and chlorite components. Examples of chlorite components include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures therefor. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Purite™ by Allergan, Inc. Other examples of oxidative preservative components includes peroxy components. For example, trace amounts of peroxy components stabilized with a hydrogen peroxide stabilizer, such as diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid, may be utilized as a preservative for use in components designed to be used in the ocular environment. Also, virtually any peroxy component may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. Examples of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, may not be stabilized utilizing the present system. See, for example, Martin et al U.S. Pat. No. 5,725,887, the disclosure of which is incorporated in its entirety herein by reference.

Preservatives other than oxidative preservative components may be included in the compositions. The choice of preservatives may depend on the route of administration. Preservatives suitable for compositions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic compositions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds and the like known generically as "benzalkonium chloride." For compositions to be administered by inhalation, however, the preferred preservative is chlorbutol and the like. Other preservatives which may be used, especially for compositions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and mixtures thereof, such as the mixture of methyl, ethyl, propyl, butyl esters and the like which is sold under the trade name "Nipastat."

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component, a preservative component in an effective amount to at least aid in preserving, preferably in an amount effective to preserve, the compositions and a liquid carrier component. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which (1) do not substantially or significantly detrimentally affect the alpha-2-adrenergic agonist components in the compositions or the patients to whom the compositions are administered, and (2) are substantially biologically acceptable and chemically stable. Such compositions in accordance with the present invention comprise an alpha-2-adrenergic agonist component, an oxy-chloro component, and a liquid carrier component, and preferably are substantially free of cyclodextrins.

The carrier components useful in the present invention are selected to be non-toxic and have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. In one embodiment, the carrier component is a liquid carrier. In a preferred embodiment, the carrier component is a liquid aqueous carrier component. A particularly useful aqueous liquid carrier component is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution. The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5. The liquid medium preferably has an ophthalmically acceptable tonicity level, for example, of at least about 200 mOsmol/kg, more preferably in the range of about 200 to about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the carrier component substantially

corresponds to the tonicity of the fluids of the eye, in particular the human eye.

In one embodiment, the carrier components containing the SECs and the alpha-2-adrenergic agonist components may have viscosities of more than about 0.01 centipoise (cps) at 25° C., preferably more than about 1 cps at 25° C., even more preferably more than about 10 cps at 25° C. In a preferred embodiment, the composition has a viscosity of about 50 cps at 25° C. and comprises a conventional buffer saline solution, a carboxymethylcellulose and a Brimonidine tartrate.

In order to insure that the pH of the aqueous liquid carrier component, and thus the pH of the composition, is maintained within the desired range, the aqueous liquid carrier component may include at least one buffer component. Although any suitable buffer component may be employed, it is preferred to select such component so as not to produce a significant amount of chlorine dioxide or evolve significant amounts of gas, such as CO_2. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components are advantageously used in the present invention.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid aqueous carrier component and do not have deleterious or toxic properties which could harm the human or animal to whom the present compositions are administered. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring agents, surface active agents, thickeners, lubricants, and the like, for example, such additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gun tragacanth and gun acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof. Such aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gun tragacanth, naturally-occurring phosphatides, for example, soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

In one broad aspect of the invention, complexes are formed in the present compositions. In one embodiment, the complexes include at least one monomer unit of a quinoxaline component. Examples of quinoxaline components include quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts thereof, esters thereof, other derivatives thereof, and the like and mixtures thereof. For example, in one embodiment, a complex of the present invention may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units. In another embodiment, the complex may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units and Brimonidine tartrate monomer units.

In a preferred embodiment, the complexes of the present invention are dimers. For example, a dimer in accordance with the present invention may include a quinoxaline and a 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Preferably, a dimer in accordance with the present invention includes two Brimonidine tartrate monomer units.

Without wishing to limit the invention to any theory or mechanism of operation, it is believed that any peroxide forming agent or strong oxidizing agent such as the oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof may facilitate the formation of the complexes, preferably complexes of alpha-2-adrenergic agonist components. For example, dimers of Brimonidine tartrate monomer units are believed to be formed in the presence of chlorites, preferably stabilized chlorine dioxide.

Furthermore, it is believed that the interactions between the monomers which serve to hold the monomers or monomer subunits together to form a complex, preferably an oligomer and more preferably a dimer, may include, but not limited to, covalent bonding, ionic bonding, hydrophobic bonding, electrostatic bonding, hydrogen bonding, other chemical and/or physical interactions, and the like and combinations thereof. Such complexes may disassociate in liquid, for example, aqueous liquid, media. In one embodiment, the monomers or monomer subunits are held together by other than covalent bonding. In one embodiment, the monomers or monomer subunits are held together by electrostatic bonding or forces.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Brimonidine tartrate has a pKa of about 7.78. The pH-solubility profile of 0.5% (w/v) Brimonidine tartrate in a formulation, Ophthalmic Solution, was established in the pH range of about 5 to about 8 at 23 ° C. Table 1. It will be understood that concentrations of adrenergic agonists other than 0.5% may be used, so long as they have therapeutic activity. Likewise, the temperature may be varied, for example, solubility curves may be performed at 37° C. (98.6° F.). The formulation vehicle was prepared by first dissolving polyvinyl alcohol (PVA) in water. The PVA was added to approximately ⅓ of the required total amount of purified water with constant stirring. The slurry was stirred for 20–30 minutes and then heated to 80–95° C. with constant stirring. The mixture was removed from the heat source within 1 hour after having reached the temperature of 80–90° C. and stirred for an additional 10 minutes to ensure homogeneity (Part I). The other ingredients of the Ophthalmic Solution, except for Brimonidine tartrate, were dissolved in a separate container with an additional ⅓ of the required total amount of purified water (Part II). The PVA mixture (Part I) was then quantitatively transferred to Part II using several rinse volumes of purified water. The solution was adjusted to final volume with purified water without pH adjustment.

Brimonidine tartrate was weighed and transferred to a 10 mL test tube containing 5 mL of the formulation vehicle described above. The pH of each sample was then adjusted to a desired value using dilute sodium hydroxide and/or dilute hydrochloric acid. The samples were placed in a rack on a stir plate and stirred at high speed to achieve uniform mixing for 2 days; a partition was placed between the rack and the stir plate to prevent any heat diffusion from the stir plate to the samples. The temperature of the laboratory was monitored throughout the study and was found to be 23±1° C.

At the end of two days of stirring, the pH value of each sample was measured, and then approximately 1 mL of each sample was placed in a micro centrifuge tube (polypropylene) and centrifuged at 4,000 rpm for 10 minutes. The supernatant was filtered through a 1 μm filter unit (Whatman, 13 mm, PTFE). The first 3–4 drops of the filtrate were discarded; the rest of the filtrate was received and diluted quantitatively with HPLC mobile phase. The dilute sample was then injected directly on the HPLC column (Dupont Zorbax, 250 mm×4.6 mm, 5 μm) for Brimonidine tartrate assay in order to quantify the amount of Brimonidine tartrate. A control of 10.05% Brimonidine tartrate was prepared in the formulation vehicle at pH 6.3–6.5 and assayed before (untreated) and after (treated) centrifugation and filtration. This was done to evaluate the potential loss of Brimonidine tartrate in these two steps of the sample preparation. To ensure reproducibility, the study was repeated on consecutive days.

TABLE I

0.5% Brimonidine tartrate in Ophthalmic Solution.

Ingredient	Percent (w/v)
Brimonidine tartrate	0.50
Benzalkonium Chloride, NF	0.0050
Polyvinyl Alcohol, USP	1.4
Sodium Chloride, USP	0.66
Sodium Citrate, Dihydrate, USP	0.45
Hydrochloric Acid, NF or Sodium Hydroxide, NF for pH adjustment	5–8
Purified Water, USP	QS

The solubility data for Brimonidine tartrate in the formulation vehicles are presented in Table II. The results show that the solubility of Brimonidine tartrate is highly pH-dependent and spans more than two orders of magnitude over the pH range of 5–8. The solubility decreases sharply as the pH increases. The results for the treated and untreated controls are very close, suggesting that centrifugation and filtration does not cause any significant loss of Brimonidine tartrate. The two solubility profiles obtained on consecutive days agree with each other.

TABLE II

Solubility of Brimonidine tartrate in the Ophthalmic Solution Over pH Range of 5 to 8.

	STUDY 1		STUDY 2	
Sample	pH[a]	Solubility[e]	pH[a]	Solubility[e]
1	5.55	≧164.4[b]	5.50	≧200.6[b]
2	5.92	132.6	5.92	160.8
3	6.14	30.4	6.06	50.1
4	6.57	7.55	6.90	3.19
5	7.00	2.69	7.40	1.19
6	7.45	1.17	7.77	0.63
7	7.83	0.62	7.86	0.58
8	—	—	7.88	0.54
Control/ (untreated)	—	0.486[c]	—	—
Control/ (treated)	—	0.484[d]	—	—

[a]Measured after stirring for two-days before sample withdrawal for centrifugation and filtration.
[b]Represents theoretical concentration based on sample weight. The sample solution was clear indicating that all of the Brimonidine tartrate has dissolved.
[c]Concentration of Brimonidine tartrate in control before centrifugation and filtration step.
[d]Concentration of Brimonidine tartrate in control after centrifugation and filtration step.
[e]% w/v.

EXAMPLE 2

The pH-solubility profiles of Brimonidine tartrate in compositions (solutions) containing SECs and oxy-chloro components were determined. Particularly, the effects of sodium carboxymethylcellulose (CMC), an SEC, on the solubility of Brimonidine tartrate at various pH conditions were determined. The various concentrations of CMC tested with Brimonidine tartrate were 0%, 0.056%, 0.17%, 0.5%, 1.5% (w/v), Table III.

The samples tested also contained isotonic components, buffer components, and stabilized chlorine dioxide (Purite™), Table III. Sodium carboxymethyl-cellulose, sodium chloride, potassium chloride, calcium chloride dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

TABLE III

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	
Brimonidine tartrate	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
CMC	0.0%	0.058%	0.17%	0.5%	1.5%	(w/v)
Stabilized chlorine dioxide[a]	0.005%	0.005%	0.005%	0.005%	0.005%	(w/v)
Sodium chloride	0.58%	0.58%	0.58%	0.58%	0.58%	(w/v)
Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)
Calcium chloride, dihydrate	0.02%	0.02%	0.02%	0.02%	0.02%	(w/v)
magnesium chloride, hexahydrate	0.006%	0.006%	0.006%	0.006%	0.006%	(w/v)
boric acid	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
sodium tetraborate, decahydrate	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)

[a]Sold under the trademark Purite ™ by Allergan, Inc.

Each sample (1 through 5) was subjected to a range of pH's from about 7 to about 10. The vials containing the sample solutions were placed on a laboratory rotator and left for equilibration for fifteen days at room temperature (~21° C.). The sample solutions were filtered using a 25 mm diameter polysulfone cellulose acetate syringe type filter with 0.45 μm pore size. The filtered solutions were assayed for Brimonidine.

Conventional HPLC and detection techniques were used to detect and determine the concentrations of soluble Brimonidine tartrate. Table IV. The solubility is plotted against pH for each CMC concentration. The experimental data points were fitted to a modified Henderson-Hasselbalch equation using a nonlinear least squares routine (Deltagraph version 4.0 DeltaPoint, Inc.), FIG. **1**. The R^2 values show the goodness of fit between the experimental values and the theoretical equation to be better than 0.991.

TABLE IV

	Solubility of Brimonidine tartrate (%)				
pH	0% CMC	0.056% CMC	0.17% CMC	0.5% CMC	1.5% CMC
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
7.56				0.1451	
7.68	0.0786				
7.77		0.0721			
7.81			0.0735		
8.10					0.0498
8.46				0.0313	
8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

FIG. **1** clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.056% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.5%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

EXAMPLE 3

Brimonidine tartrate dimers.

Brimonidine tartrate is added to a test tube containing a composition including chlorite. The test tube was allowed to equilibrate for ten days. Samples obtained from the test tube is analyzed. It is observed that a portion of the Brimonidine tartrate monomer units conjugated to form dimers.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

What is claimed is:

1. A therapeutically effective aqueous composition comprising:

a therapeutically active alpha-2-adrenergic agonist component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a salt thereof, and an ester thereof in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

a polyanionic solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

2. The composition of claim **1** wherein the therapeutically active component comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

3. The composition of claim **1** wherein the therapeutically active component is substantially unionized.

4. The composition of claim **1** wherein the therapeutically active component is substantially unionized in a biological environment to which the composition is administered.

5. The composition of claim **1** wherein the therapeutically active component has increased diffusion through a lipid membrane relative to an identical therapeutically active component in a similar composition the solubility enhancing component.

6. The composition of claim 1 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the therapeutically active component relative to the solubility in a biological environment of an identical therapeutically active component in a similar composition without the solubility enhancing component.

7. The composition of claim 1 wherein said polyanionic component is selected from the group consisting of anionic cellulose derivatives, anionic polymers derived from acrylic acid, anionic polymers derived from methacrylic acid, anionic polymers derived from alginic acid, anionic polymers derived from amino acids and mixtures thereof.

8. The composition of claim 1 wherein the solubility enhancing component is selected from the group consisting of anionic cellulose derivatives and mixtures thereof.

9. The composition of claim 1 wherein the solubility enhancing component is selected from the group consisting of carboxymethylcelluloses and derivatives thereof.

10. The composition of claim 1 wherein the solubility enhancing component is present in an amount in a range of about 0.1% (w/v) to about 30% (w/v).

11. The composition of claim 1 wherein the solubility enhancing component is present in an amount in a range of about 0.2% (w/v) to about 10% (w/v).

12. The composition of claim 1 wherein the solubility enhancing component is present in an amount in a range of about 0.2% (w/v) to about 0.6% (w/v).

13. The composition of claim 1 which has a pH of about 7 or greater.

14. The composition of claim 1 which has a pH in a range of about 7 to about 9.

15. The composition of claim 1 which is ophthalmically acceptable.

16. A therapeutically effective aqueous composition comprising:

a therapeutically active component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a salt thereof, and an ester thereof in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

an anionic cellulose derivative in an amount effective to increase the solubility of the therapeutically active component.

17. The composition of claim 16 wherein the alpha-2-adrenergic agonist component comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

18. The composition of claim 16 wherein the anionic cellulose derivative comprises carboxymethylcellulose.

19. The composition of claim 16 wherein the anionic cellulose derivative is present in an amount in a range of about 0.2% (w/v) to about 0.6% (w/v).

20. A therapeutically effective aqueous composition comprising:

a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

an anionic solubility enhancing component in an amount effective to increase the solubility of the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

21. The composition of claim 20 wherein the solubility enhancing component comprises a carboxymethylcellulose.

22. The composition of claim 20 which is ophthalmically acceptable.

23. The composition of claim 1 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

24. The composition of claim 23 in which the preservative comprises benzalkonium chloride.

25. The composition of claim 23 in which the preservative comprises an oxy-chloro component.

26. The composition of claim 23 in which the preservative comprises a chlorite component.

27. The composition of claim 16 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

28. The composition of claim 27 which the preservative comprises benzalkonium chloride.

29. The composition of claim 27 in which the preservative comprises an oxy-chloro component.

30. The composition of claim 27 in which the preservative comprises a chlorite component.

31. The composition of claim 20 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

32. The composition of claim 31 in which the preservative comprises benzalkonium chloride.

33. The composition of claim 31 in which the preservative comprises an oxy-chloro component.

34. The composition of claim 31 in which the preservative comprises a chlorite component.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

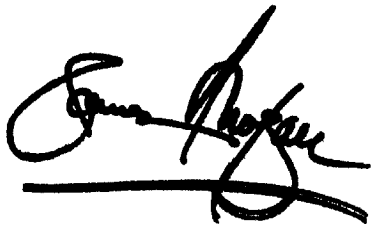
PATENT NO. : 6,627,210 B2
DATED : September 30, 2003
INVENTOR(S) : Olejnik et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5,
Line 52, delete "disclose" and insert in place thereof -- disclosed --

Signed and Sealed this

Sixth Day of January, 2004



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US006673337B2

(12) **United States Patent**
Olejnik et al.

(10) **Patent No.: US 6,673,337 B2**
(45) **Date of Patent: *Jan. 6, 2004**

(54) **COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS**

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(73) Assignee: **Allergan, Inc.**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 16 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/299,386**

(22) Filed: **Nov. 19, 2002**

(65) **Prior Publication Data**

US 2003/0087893 A1 May 8, 2003

Related U.S. Application Data

(62) Division of application No. 09/904,018, filed on Jul. 10, 2001.
(60) Provisional application No. 60/218,200, filed on Jul. 14, 2000.

(51) **Int. Cl.**[7] **A61K 31/74**
(52) **U.S. Cl.** **424/78.04**; 424/400; 514/249
(58) **Field of Search** 424/661, 427, 424/422, 78.04, 400; 514/58, 249

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Primary Examiner—Thurman K. Page
Assistant Examiner—Rachel M. Bennett
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(57) **ABSTRACT**

Compositions useful for improving effectiveness of alpha-2-adrenergic agonist components include carrier components, alpha-2-adrenergic agonist components, solubility enhancing components which aid in solubilizing the alpha-2-adrenergic agonist components. In one embodiment, the alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. In another embodiment, the solubility enhancing components include carboxymethylcellulose.

10 Claims, 1 Drawing Sheet

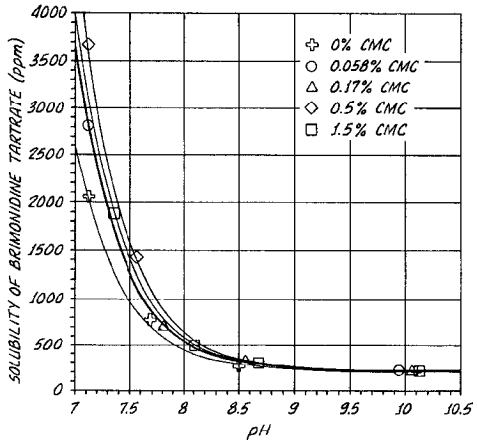
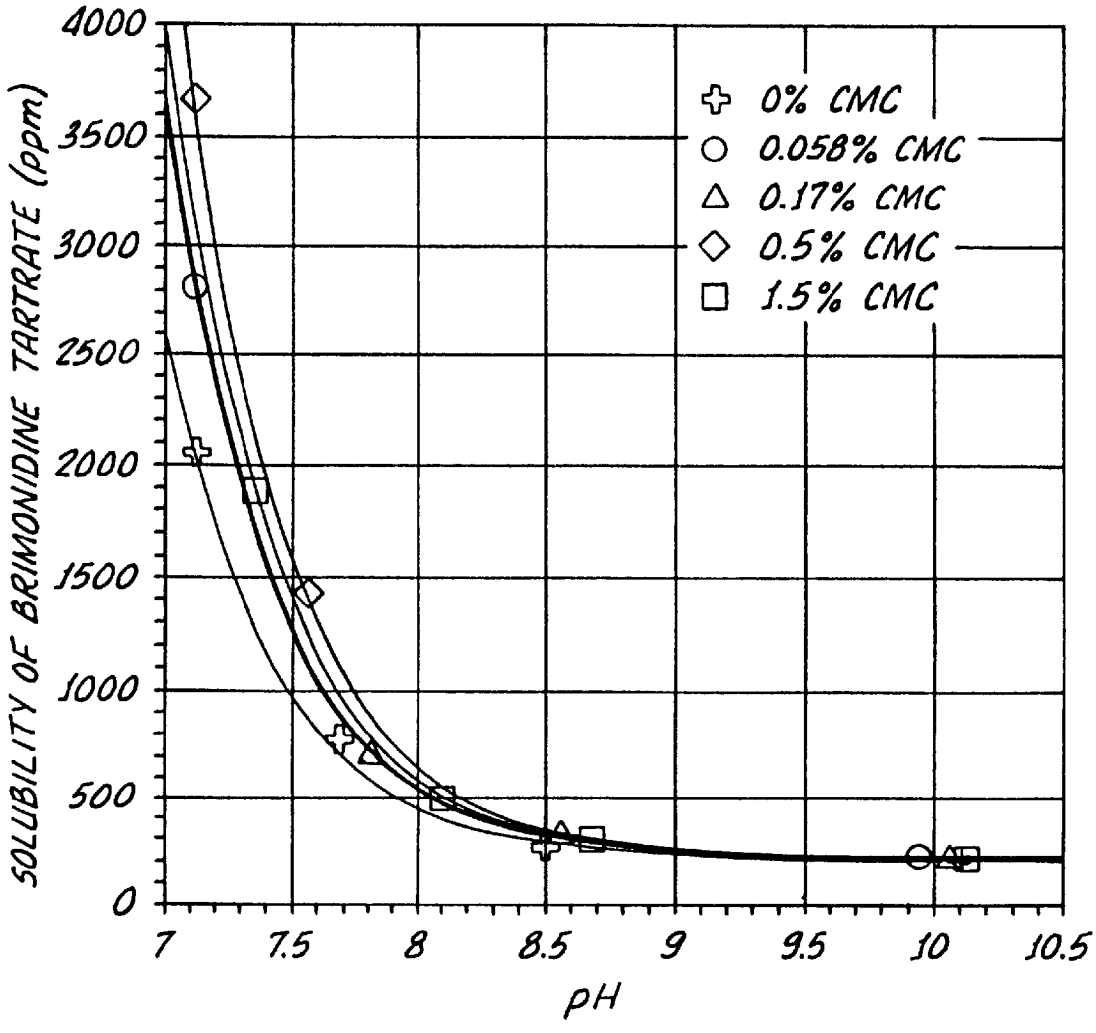


FIG. 1


SOLUBILITY OF BRIMONIDINE TARTRATE (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0
7
7.5
8
8.5
9
9.5
10
10.5
pH
0% CMC
0.058% CMC
0.17% CMC
0.5% CMC
1.5% CMC

COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

CROSS REFERENCE TO RELATED APPLICATION

This application is a division of application Ser. No.: 09/904,018, filed Jul. 10, 2001, which application claims the benefit of U.S. Provisional Application Serial No. 60/218,200 filed Jul. 14, 2000, the disclosure of each of these applications is hereby incorporated herein in its entirety by reference.

BACKGROUND OF THE INVENTION

The present invention relates to compositions containing alpha-2-adrenergic agonist components. More particularly, the invention relates to such compositions in which the alpha-2-adrenergic agonist components have enhanced solubility at the therapeutically effective concentrations.

Alpha-2-adrenergic agonist components include chemical entities, such as compounds, ions, complexes and the like, which are effective to act on or bind to Alpha-2-adrenergic receptors and provide a therapeutic effect. Alpha-2-adrenergic agonist components means the agonists themselves and any and all precursors thereof, metabolites thereof and combinations thereof. One of the continuing challenges of formulating compositions having alpha-2-adrenergic agonist components is to render such components more effective. For example, alpha-2-adrenergic agonist components in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration.

Additionally, the dispensed or administered alpha-2-adrenergic agonist components should advantageously be soluble in biological systems or environments, for example, for effective or enhanced in vivo diffusion through cell membranes or lipid bilayers. Some alpha-2-adrenergic agonist components with higher pKa's, for example, greater than about 7, tend to diffuse very well through lipid membranes at pH valves near their pka, because in such circumstances they are predominantly unionized in neutral to alkaline biological environments. However, some of these alpha-2-adrenergic agonist components become insoluble at neutral to alkaline biological pH's. Such insolubility may decrease membrane diffusion capabilities, rendering the alpha-2-adrenergic agonist components less effective and/or their therapeutic effects more variable at a given dosage. Furthermore, solubilized alpha-2-adrenergic agonist components provide other benefits, for example, reduced irritation to tissues that interact with alpha-2-adrenergic agonist components.

There continues to be a need for new compositions containing alpha-2-adrenergic agonist components.

SUMMARY OF THE INVENTION

New alpha-2-adrenergic agonist component-containing compositions have been discovered. The present compositions contain certain materials which are effective in at least aiding or assisting in solubilizing the alpha-2-adrenergic agonist components in the compositions, and preferably in environments to which the compositions are administered or introduced, for example, biological environments, such as the human eye. Preferably, solubilization of the alpha-2-adrenergic agonist components in accordance with the present invention facilitates transport of such components across lipid membranes. Also, preferably such solubilization

allows the provision of more reliable and reproducible dosage forms of the drug. In addition, alpha-2-adrenergic agonist component-containing compositions have been discovered which include preservatives which provide substantial advantages, for example, reduced adverse interactions with the alpha-2-adrenergic agonist components and/or with the patients to whom the compositions are administered, while maintaining preservative effectiveness.

The present compositions preferably enhance the effectiveness of alpha-2-adrenergic agonist components by increasing the apparent water solubility of the alpha-2-adrenergic agonist components, preferably at pH's higher than neutral. The present compositions include, in addition to the adrenergic agonist components, solubility enhancing components (SECs) in amounts effective to enhance the solubility of the alpha-2-adrenergic agonist components. Preferably, the alpha-2-adrenergic agonist components are more soluble in the present compositions having, for example, pH's of about 7 or greater, relative to similar compositions without the SECs. In another embodiment, the alpha-2-adrenergic agonist components of the present compositions are more soluble in neutral, preferably alkaline, biological environments into which the compositions are administered relative to alpha-2-adrenergic agonist components in similar compositions without the SECs.

In one embodiment, the alpha-2-adrenergic agonist components include imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. Preferably, the alpha-2-adrenergic agonist components include quinoxaline components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and biologically compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is referred to as "Brimonidine tartrate."

In a preferred embodiment, the alpha-2-adrenergic agonist components, such as those listed above, are specific for the alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and/or alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonist components are unionized in the compositions. Preferably, the alpha-2-adrenergic agonist components are also unionized in the biological environment into which the compositions are administered.

In a useful embodiment, the SEC includes a polyanionic component. As used herein, the term "polyanionic component" refers to a chemical entity, for example, an ionically charged species, such as an ionically charged polymeric material, which includes more than one discrete anionic charge, that is multiple discrete anionic charges. Preferably, the polyanionic component is selected from polymeric materials having multiple anionic charges, and mixtures thereof.

Particularly useful polyanionic components are selected from anionic polymers derived from acrylic acid (meaning to include polymers from acrylic acid, acrylates and the like and mixtures thereof), anionic polymers derived from methacrylic acid (meaning to include polymers from methacrylic acid, methacrylates, and the like and mixtures thereof), anionic polymers derived from alginic acid (meaning to

include alginic acid, alginates, and the like and mixtures thereof), anionic polymers of amino acids (meaning to include polymers of amino acids, amino acid salts, and the like and mixtures thereof), and the like, and mixtures thereof. Very useful polyanionic components are those selected from anionic cellulose derivatives and mixtures thereof, especially carboxymethylcelluloses.

The polyanionic component preferably is sufficiently anionic to interact with or otherwise affect, in particular increase, the solubility of the alpha-2-adrenergic components. This interaction preferably is sufficient to render the alpha-2-adrenergic components substantially completely soluble at therapeutically effective concentrations. The amount of SEC in the composition preferably is in the range of about 0.1% (w/v) to about 30% (w/v), more preferably about 0.2% (w/v) to about 10% (w/v), and even more preferably about 0.2% (w/v) to about 0.6% (w/v).

The compositions include carrier components, for example, aqueous liquid carrier components. In one embodiment, the compositions have pH's of about 7 or greater, preferably about 7 to about 9, and are ophthalmically acceptable.

In a preferred embodiment, a composition is provided which includes an alpha-2-adrenergic agonist component in an amount effective to provide at least one therapeutic benefit to a patient to whom the composition is administered, an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component and an aqueous liquid carrier component. The alpha-2-adrenergic agonist component preferably comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. The anionic cellulose derivative preferably comprises a carboxymethylcellulose. The concentration of the anionic cellulose derivative in the composition should be about 0.2% (w/v) to about 0.6% (w/v).

In a preferred embodiment, the present compositions are ophthalmically acceptable, e.g. the compositions do not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered.

In one broad aspect of the invention, complexes are formed in the compositions. In one embodiment, the complexes include monomer units derived from at least one quinoxaline component. In a preferred embodiment, the complexes of the present invention are dimers. In a particularly preferred embodiment, the complexes are complexes, especially dimers, of Bromodidine tartrate.

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component and a preservative component in an effective amount to at least aid in preserving the compositions. Preferably, the preservative components include oxychloro components, such as compounds, ions, complexes and the like which are biologically acceptable, chemically stable and do not substantially or significantly detrimentally affect the an alpha-2-adrenergic agonist component in the compositions or the patients to whom the compositions are administered. Such compositions preferably are substantially free of cyclodextrins in the compositions or the patients to whom the compositions are administered.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art.

Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** is a graph of soluble Brimonidine tartrate verses pH at various carboxymethylcellulose concentrations.

DETAILED DESCRIPTION OF THE INVENTION

Compositions comprising alpha-2-adrenergic agonist components and SECs are provided. The alpha-2-adrenergic agonist components in the present compositions are made more soluble and may be more effectively utilized as therapeutic agents. The SECs employed in the present compositions may be effective in the solubilization of ionized alpha-2-adrenergic agonist components, unionized alpha-2-adrenergic agonist components or both. The present compositions include liquid carrier components and have the characteristics of liquid, for example, aqueous liquid, solutions.

Preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's greater than 7, as compared to identical alpha-2-adrenergic agonist components, at comparable concentrations, in similar compositions without the SECs. More preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's in the range of about 7 to about 10 and, as compared to identical alpha-2-adrenergic agonist components in similar compositions, at comparable concentrations, without the SECs.

Without wishing to be limited by any theory or mechanism of operation, it is believed that solubilized alpha-2-adrenergic agonist components are better able to cross the lipid membranes relative to unsolubilized alpha-2-adrenergic agonist components. It is further believed that the solubilized alpha-2-adrenergic agonist components are physically smaller and are therefore more able to physically permeate or diffuse through the lipid membranes.

In one embodiment, the SECs of this invention are capable of solubilizing the alpha-2-adrenergic agonist components in the biological environments into which they are introduced at therapeutically effective concentrations. Preferably, the biological environments into which the present compositions are introduced have pH's ranging from about 7 to about 9. For example, a composition comprising a SEC and an alpha-2-adrenergic agonist component may be administered to the cornea of an eye, which has a pH of about 7, wherein the alpha-2-adrenergic agonist component is substantially solubilized at the administered area. Furthermore, in one embodiment, the alpha-2-adrenergic agonist components solubilized by SECs at the administered area diffuse through biological lipid membranes more readily than alpha-2-adrenergic agonist components which are not solubilized by SECs. The solubilization of alpha-2-adrenergic agonist components preferably reduces irritation to sensitive tissues in contact or interacting with the alpha-2-adrenergic agonist components.

The presently useful alpha-2-adrenergic agonist components preferably are chosen to benefit from the presence of the SECs. In general, the alpha-2-adrenergic agonist components are provided with increased apparent solubility, preferably increased apparent water solubility, by the presence of the SECs.

Examples of alpha-2-adrenergic agonist components include molecules containing amines. Preferably, the alpha-

2-adrenergic agonist components are amine-containing molecules with pKa's of greater than about 7, more preferably about 7 to about 9.

Alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. As used herein, the term alpha-2 adrenergic agonist includes chemical entities, such as compounds, ions, complexes and the like, that produce a net sympatholytic response, resulting in increased accommodation, for example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or for example, to postsynaptic alpha-2 receptors on smooth muscle cells. A sympatholytic response is characterized by the inhibition, diminishment, or prevention of the effects of impulses conveyed by the sympathetic nervous system. The alpha-2 adrenergic agonists of the invention bind to the alpha-2 adrenergic receptors presynaptically, causing negative feedback to decrease the release of neuronal norepinephrine. Additionally, they also work on alpha-2 adrenergic receptors postsynaptically, inhibiting beta-adrenergic receptor-stimulated formation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2 adrenergic receptors on other intracellular pathways. Activity at either pre- or postsynaptic alpha-2 adrenergic receptors will result in a decreased adrenergic influence. Decreased adrenergic influence results in increased contraction resulting from cholinergic innervations. Alpha-2 adrenergic agonists also include compounds that have neuroprotective activity. For example, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is an alpha-2-adrenergic agonist which has a neuroprotective activity through an unknown mechanism.

Without limiting the invention to the specific groups and compounds listed, the following is a list of representative alpha-2 adrenergic agonists useful in this invention: iminoimidazolines, including clonidine, apraclonidine; imidazolines, including naphazoline, xymetazoline, tetrahydrozoline, and tramazoline; imidazoles, including detomidine, medetomidine, and dexmedetomidine; azepines, including B-HT 920 (6-allyl-2-amino-5,6,7,8 tetrahydro-4H-thiazolo[4,5-d]-azepine and B-HT 933; thiazines, including xylazine; oxazolines, including rilmenidine; guanidines, including guanabenz and guanfacine; catecholamines; and the like and derivatives thereof.

Particularly useful alpha-2-adrenergic agonists include quinoxaline components. In one embodiment, the quinoxaline components include quinoxaline, derivatives thereof and mixtures thereof. Preferably, the derivatives of quinoxaline include (2-imidozolin-2-ylamino) quinoxaline. More preferably, the derivatives of quinoxaline include 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline The "halide" of the 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline may be a fluorine, a chlorine, an iodine, or preferably, a bromine, to form 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline . Even more preferably, the derivatives of quinoxaline to be used in accordance with this invention include a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline , or Brimonidine tartrate.

Other useful quinoxaline derivatives are well known. For example, useful derivatives of a quinoxaline include the ones disclose by Burke et al U.S. Pat. No. 5,703,077. See also Danielwicz et al U.S. Pat. No. 3,890,319. Each of the disclosures of Burke et al and Danielwicz et al is incorporated in its entirety by reference herein.

The quinoxaline and derivatives thereof, for example Brimonidine tartrate, are amine-containing and preferably have pKa's of greater than 7, preferably about 7.5 to 9.

Analogs of the foregoing compounds that function as alpha-2 adrenergic agonists also are specifically intended to be embraced by the invention.

Preferably, the alpha-2-adrenergic agonists, for example the ones listed above, are effective toward activating alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonists, for example Brimonidine tartrate, are substantially unionized in the compositions. In another embodiment, the adrenergic compounds are substantially unionized in the environment to which they are administered, for example the cornea. Without wishing to be limited by any theory or mechanism of action, it is believed that the unionized forms of the adrenergic compounds facilitate their permeation across membrane lipid bilayers.

Any suitable SEC may be employed in accordance with the present invention. In one embodiment, the SECs include pyrrolinidone components. Examples of pyrrolinidone components are polyvinylpyrrolinidones and derivatives thereof. In a preferred embodiment, the SECs include polyanionic components. The useful polyanionic components include, but are not limited to, those materials which are effective in increasing the apparent solubility, preferably water solubility, of poorly soluble alpha-2-adrenergic agonist components and/or enhance the stability of the alpha-2-adrenergic agonist components and/or reduce unwanted side effects of the alpha-2-adrenergic agonist components. Furthermore, the polyanionic component is preferably ophthalmically acceptable at the concentrations used. Additionally, the polyanionic component preferably includes three (3) or more anionic (or negative) charges. In the event that the polyanionic component is a polymeric material, it is preferred that each of the repeating units of the polymeric material include a discrete anionic charge. Particularly useful anionic components are those which are water soluble, for example, soluble at the concentrations used in the presently useful liquid aqueous media, such as a liquid aqueous medium containing the alpha-2-adrenergic components.

The polyanionic component is preferably sufficiently anionic to interact with the alpha-2-adrenergic agonist component. Such interaction is believed to be desirable to solubilize the alpha-2-adrenergic agonist component and/or to maintain such alpha-2-adrenergic agonist component soluble in the carrier component, for example a liquid medium.

Polyanionic components also include one or more polymeric materials having multiple anionic charges. Examples include:

- metal carboxymethylstarchs
- metal carboxymethylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - metal acrylates and methacrylates
  - alginic acid
  - metal alginates
  - vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - p-styrenesulfonic acid

metal p-styrenesulfonate
2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

In another embodiment, the polyanionic components include anionic polysaccharides which tend to exist in ionized forms at higher pH's, for example, pH's of about 7 or higher. The following are some examples of anionic polysaccharides which may be employed in accordance with this invention.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose.

Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks.

Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of which can be sulfated or nonsulfated, joined by alternating 1–3 and beta 1–4 glycosidic linkages. Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss.

Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water.

Other anionic polysaccharides found useful in the present invention are hydrophilic colloidal materials and include the natural gums such as gellan gum, alginate gums, i.e., the ammonium and alkali metal salts of alginic acid and mixtures thereof. In addition, chitosan, which is the common name for deacetylated chitin is useful. Chitin is a natural product comprising poly-(N-acetyl-D-glucosamine). Gellan gum is produced from the fermentation of pseudomonas elodea to yield an extracellular heteropolysaccharide. The alginates and chitosan are available as dry powders from Protan, Inc., Commack, N.Y. Gellan gum is available from the Kelco Division of Merk & Co., Inc., San Diego, Calif.

Generally, the alginates can be any of the water-soluble alginates including the alkali metal alginates, such as sodium, potassium, lithium, rubidium and cesium salts of alginic acid, as well as the ammonium salt, and the soluble alginates of an organic base such as mono-, di-, or triethanolamine alginates, aniline alginates, and the like. Generally, about 0.2% to about 1% by weight and, preferably, about 0.5% to about 3.0% by weight of gellan, alginate or chitosan ionic polysaccharides, based upon the total weight of the composition, are used to obtain the gel compositions of the invention.

Preferably, the anionic polysaccharides are cyclized. More preferably, the cyclized anionic polysaccharides include less than ten monomer units. Even more preferably, the cyclized polysaccharides include less than six monomer units.

In one embodiment, a particularly useful group of cyclized anionic polysaccharides includes the cyclodextrins. Examples of the cyclodextrin group include, but are not limited to: α-cyclodextrin, derivatives of α-cyclodextrin, β-cyclodextrin, derivatives of β-cyclodextrin, γ-cyclodextrin, derivatives of γ-cyclodextrin, carboxymethyl-β-cyclodextrin, carboxymethyl-ethyl-β-cyclodextrin, diethyl-β-cyclodextrin, dimethyl-β-cyclodextrin, methyl-β-cyclodextrin, random methyl-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and the like and mixtures thereof. Sulfobutylether-β-cyclodextrin is a preferred cyclized anionic polyasaccharide in accordance with the present invention. It is advantageous that the SEC's, including the above mentioned cyclodextrins, employed in this invention be, at the concentration employed, non-toxic to the mammal, human, to inhibit the present incorporation is administered. As used herein, the term "derivatives" as it relates to a cyclodextrin means any substituted or otherwise modified compound which has the characteristic chemical structure of a cyclodextrin sufficiently to function as a cyclodextrin component, for example, to enhance the solubility and/or stability of active components and/or reduce unwanted side effects of the active components and/or to form inclusive complexes with active components, as described herein.

Although cyclodextrins and/or their derivatives may be employed as SECs, one embodiment of the invention may include SECs other than cyclodextrins and/or their derivatives.

A particularly useful and preferred class of polyanionic component includes anionic cellulose derivatives. Anionic cellulose derivatives include metal carboxymethylcelluloses, metal carboxymethylhydroxyethylcelluloses and hydroxypropylmethylcelluloses and derivatives thereof.

The present polyanionic components often can exist in the unionized state, for example, in the solid state, in combination with a companion or counter ion, in particular a plurality of discrete cations equal in number to the number of discrete anionic charges so that the unionized polyanionic component is electrically neutral. For example, the present unionized polyanionic components may be present in the acid form and/or in combination with one or more metals. Since the polyanionic components are preferably ophthalmically acceptable, it is preferred that the metal associated with the unionized polyanionic component be ophthalmically acceptable in the concentrations used. Particularly useful metals include the alkali metals, for example, sodium and potassium, the alkaline earth metals, for example, calcium and magnesium, and mixtures thereof. Sodium is very useful to provide the counter ion in the unionized polyanionic component. Polyanionic components which, in the unionized states, are combined with cations other than H^+ and metal cations can be employed in the present invention.

The amount of SEC in the present compositions is not of critical importance so long as solubility at the alpha-2-adrenergic agonist component is at least somewhat increased and is present in a biologically acceptable amount. Such amount should be effective to perform the desired function or functions in the present composition and/or after administration to the human or animal. In one embodiment, the amount of SEC, preferably the polyanionic component, is sufficient to complex at least in a major amount, and more preferably substantially all, of the alpha-2-adrenergic agonist component in the present composition. In one useful embodiment, the amount of polyanionic component in the present composition is in the range of about 0.1% to about 30% (w/v) or more of the composition. Preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 10% (w/v). More preferably, the amount of polyanionic component is in the range of about 0.2%

(w/v) to about 0.6% (w/v). Even more preferably, the polyanionic component is carboxymethylcellulose and is present in the composition in the range of about 0.2% (w/v) to about 0.6% (w/v). A particularly useful concentration of carboxymethylcellulose in the present compositions is about 0.5%.

In one embodiment, the SECs, for example a carboxymethylcellulose, assist in solubilizing the alpha-2-adrenergic agonist components in the compositions. Although the SECs are capable aiding in the solubilization of ionized alpha-2-adrenergic agonist components, it is preferable that the SECs used in this invention could assist in the solubilization of unionized alpha-2-adrenergic agonist components. For example, in one embodiment, carboxymethylcellulose may help solubilize ionized alpha-2-adrenergic agonist components. In another embodiment, carboxymethylcellulose may help solubilize unionized alpha-2-adrenergic agonist components. In a preferred embodiment, the carboxylmethylcellulose helps solubilize ionized Brimonidine tartrate in the compositions. More preferably, the carboxylmethylcellulose helps solubilize unionized Brimonidine tartrate in the compositions.

In one embodiment, the compositions may also include preservative components or components which assist in the preservation of the composition. The preservative components selected so as to be effective and efficacious as preservatives in the present compositions, that is in the presence of polyanionic components, and preferably have reduced toxicity and more preferably substantially no toxicity when the compositions are administered to a human or animal.

Preservatives or components which assist in the preservation of the composition which are commonly used in pharmaceutical compositions are often less effective when used in the presence of solubilizing agents. In certain instances, this reduced preservative efficacy can be compensated for by using increased amounts of the preservative. However, where sensitive or delicate body tissue is involved, this approach may not be available since the preservative itself may cause some adverse reaction or sensitivity in the human or animal, to whom the composition is administered.

Preferably, the present preservative components or components which assist in the preservation of the composition, preferably the alpha-2-adrenergic agonist components therein, are effective in concentrations of less than about 1% (w/v) or about 0.8% (w/v) and may be 500 ppm (w/v) or less, for example, in the range of about 10 ppm(w/v) or less to about 200 ppm(w/v). Preservative components in accordance with the present invention preferably include, but are not limited to, those which form complexes with the polyanionic component to a lesser extent than does benzalkonium chloride.

Very useful examples of the present preservative components include, but are not limited to oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof. Specific examples of oxy-chloro components useful as preservatives in accordance with the present invention include hypochlorite components, for example hypochlorites; chlorate components, for example chlorates; perchlorate components, for example perchlorates; and chlorite components. Examples of chlorite components include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures therefor. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Purite™ by Allergan, Inc. Other examples of oxidative preservative components includes peroxy components. For example, trace amounts of peroxy components stabilized with a hydrogen peroxide stabilizer, such as diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid, may be utilized as a preservative for use in components designed to be used in the ocular environment. Also, virtually any peroxy component may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. Examples of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, may not be stabilized utilizing the present system. See, for example, Martin et al U.S. Pat. No. 5,725,887, the disclosure of which is incorporated in its entirety herein by reference.

Preservatives other than oxidative preservative components may be included in the compositions. The choice of preservatives may depend on the route of administration. Preservatives suitable for compositions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic compositions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds and the like known generically as "benzalkonium chloride." For compositions to be administered by inhalation, however, the preferred preservative is chlorbutol and the like. Other preservatives which may be used, especially for compositions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and mixtures thereof, such as the mixture of methyl, ethyl, propyl, butyl esters and the like which is sold under the trade name "Nipastat."

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component, a preservative component in an effective amount to at least aid in preserving, preferably in an amount effective to preserve, the compositions and a liquid carrier component. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which (1) do not substantially or significantly detrimentally affect the alpha-2-adrenergic agonist components in the compositions or the patients to whom the compositions are administered, and (2) are substantially biologically acceptable and chemically stable. Such compositions in accordance with the present invention comprise an alpha-2-adrenergic agonist component, an oxy-chloro component, and a liquid carrier component, and preferably are substantially free of cyclodextrins.

The carrier components useful in the present invention are selected to be non-toxic and have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. In one embodiment, the carrier component is a liquid carrier. In a preferred embodiment, the carrier component is a liquid aqueous carrier component. A

particularly useful aqueous liquid carrier component is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution. The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5. The liquid medium preferably has an ophthalmically acceptable tonicity level, for example, of at least about 200 mOsmol/kg, more preferably in the range of about 200 to about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the carrier component substantially corresponds to the tonicity of the fluids of the eye, in particular the human eye.

In one embodiment, the carrier components containing the SECs and the alpha-2-adrenergic agonist components may have viscosities of more than about 0.01 centipoise (cps) at 25° C., preferably more than about 1 cps at 25° C., even more preferably more than about 10 cps at 25° C. In a preferred embodiment, the composition has a viscosity of about 50 cps at 25° C. and comprises a conventional buffer saline solution, a carboxymethylcellulose and a Brimonidine tartrate.

In order to insure that the pH of the aqueous liquid carrier component, and thus the pH of the composition, is maintained within the desired range, the aqueous liquid carrier component may include at least one buffer component. Although any suitable buffer component may be employed, it is preferred to select such component so as not to produce a significant amount of chlorine dioxide or evolve significant amounts of gas, such as CO_2. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components are advantageously used in the present invention.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid aqueous carrier component and do not have deleterious or toxic properties which could harm the human or animal to whom the present compositions are administered. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring agents, surface active agents, thickeners, lubricants, and the like, for example, such additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gun tragacanth and gun acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof. Such aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gun tragacanth, naturally-occurring phosphatides, for example, soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

In one broad aspect of the invention, complexes are formed in the present compositions. In one embodiment, the complexes include at least one monomer unit of a quinoxaline component. Examples of quinoxaline components include quinoxaline, (2-imidozolin-2-ylamino) quinoxaline , 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline , salts thereof, esters thereof, other derivatives thereof, and the like and mixtures thereof. For example, in one embodiment, a complex of the present invention may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units. In another embodiment, the complex may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units and Brimonidine tartrate monomer units.

In a preferred embodiment, the complexes of the present invention are dimers. For example, a dimer in accordance with the present invention may include a quinoxaline and a 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Preferably, a dimer in accordance with the present invention includes two Brimonidine tartrate monomer units.

Without wishing to limit the invention to any theory or mechanism of operation, it is believed that any peroxide forming agent or strong oxidizing agent such as the oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof may facilitate the formation of the complexes, preferably complexes of alpha-2-adrenergic agonist components. For example, dimers of Brimonidine tartrate monomer units are believed to be formed in the presence of chlorites, preferably stabilized chlorine dioxide.

Furthermore, it is believed that the interactions between the monomers which serve to hold the monomers or mono-

mer subunits together to form a complex, preferably an oligomer and more preferably a dimer, may include, but not limited to, covalent bonding, ionic bonding, hydrophobic bonding, electrostatic bonding, hydrogen bonding, other chemical and/or physical interactions, and the like and combinations thereof. Such complexes may disassociate in liquid, for example, aqueous liquid, media. In one embodiment, the monomers or monomer subunits are held together by other than covalent bonding. In one embodiment, the monomers or monomer subunits are held together by electrostatic bonding or forces.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Brimonidine tartrate has a pKa of about 7.78. The pH-solubility profile of 0.5% (w/v) Brimonidine tartrate in a formulation, Ophthalmic Solution, was established in the pH range of about 5 to about 8 at 23° C. Table 1. It will be understood that concentrations of adrenergic agonists other than 0.5% may be used, so long as they have therapeutic activity. Likewise, the temperature may be varied, for example, solubility curves may be performed at 37° C. (98.6° F.). The formulation vehicle was prepared by first dissolving polyvinyl alcohol (PVA) in water. The PVA was added to approximately ⅓ of the required total amount of purified water with constant stirring. The slurry was stirred for 20–30 minutes and then heated to 80–95° C. with constant stirring. The mixture was removed from the heat source within 1 hour after having reached the temperature of 80–90° C. and stirred for an additional 10 minutes to ensure homogeneity (Part I). The other ingredients of the Ophthalmic Solution, except for Brimonidine tartrate, were dissolved in a separate container with an additional ⅓ of the required total amount of purified water (Part II). The PVA mixture (Part I) was then quantitatively transferred to Part II using several rinse volumes of purified water. The solution was adjusted to final volume with purified water without pH adjustment.

Brimonidine tartrate was weighed and transferred to a 10 mL test tube containing 5 mL of the formulation vehicle described above. The pH of each sample was then adjusted to a desired value using dilute sodium hydroxide and/or dilute hydrochloric acid. The samples were placed in a rack on a stir plate and stirred at high speed to achieve uniform mixing for 2 days; a partition was placed between the rack and the stir plate to prevent any heat diffusion from the stir plate to the samples. The temperature of the laboratory was monitored throughout the study and was found to be 23±1° C.

At the end of two days of stirring, the pH value of each sample was measured, and then approximately 1 mL of each sample was placed in a micro centrifuge tube (polypropylene) and centrifuged at 4,000 rpm for 10 minutes. The supernatant was filtered through a 1 μm filter unit (Whatman, 13 mm, PTFE). The first 3–4 drops of the filtrate were discarded; the rest of the filtrate was received and diluted quantitatively with HPLC mobile phase. The dilute sample was then injected directly on the HPLC column (Dupont Zorbax, 250 mm×4.6 mm, 5 μm) for Brimonidine tartrate assay in order to quantify the amount of Brimonidine tartrate. A control of 10.05% Brimonidine tartrate was prepared in the formulation vehicle at pH 6.3–6.5 and assayed before (untreated) and after (treated) centrifugation and filtration. This was done to evaluate the potential loss of Brimonidine tartrate in these two steps of the sample preparation. To ensure reproducibility, the study was repeated on consecutive days.

TABLE I

0.5% Brimonidine tartrate in Ophthalmic Solution.

Ingredient	Percent (w/v)
Brimonidine tartrate	0.50
Benzalkonium Chloride, NF	0.0050
Polyvinyl Alcohol, USP	1.4
Sodium Chloride, USP	0.66
Sodium Citrate, Dihydrate, USP	0.45
Hydrochloric Acid, NF or Sodium Hydroxide, NF for pH adjustment	5–8
Purified Water, USP	QS

The solubility data for Brimonidine tartrate in the formulation vehicles are presented in Table II. The results show that the solubility of Brimonidine tartrate is highly pH-dependent and spans more than two orders of magnitude over the pH range of 5–8. The solubility decreases sharply as the pH increases. The results for the treated and untreated controls are very close, suggesting that centrifugation and filtration does not cause any significant loss of Brimonidine tartrate. The two solubility profiles obtained on consecutive days agree with each other.

TABLE II

Solubility of Brimonidine tartrate in the Ophthalmic Solution Over pH Range of 5 to 8.

	STUDY 1		STUDY 2	
Sample	pH[a]	Solubility[e]	pH[a]	Solubility[e]
1	5.55	≧164.4[b]	5.50	≧200.6[b]
2	5.92	132.6	5.92	160.8
3	6.14	30.4	6.06	50.1
4	6.57	7.55	6.90	3.19
5	7.00	2.69	7.40	1.19
6	7.45	1.17	7.77	0.63
7	7.83	0.62	7.86	0.58
8	—	—	7.88	0.54
Control/ (untreated)	—	0.486[c]	—	—
Control/ (treated)	—	0.484[d]	—	—

[a]Measured after stirring for two-days before sample withdrawal for centrifugation and filtration.
[b]Represents theoretical concentration based on sample weight. The sample solution was clear indicating that all of the Brimonidine tartrate had dissolved.
[c]Concentration of Brimonidine tartrate in control before centrifugation and filtration step.
[d]Concentration of Brimonidine tartrate in control after centrifugation and filtration step.
[e]% w/v.

EXAMPLE 2

The pH-solubility profiles of Brimonidine tartrate in compositions (solutions) containing SECs and oxy-chloro components were determined. Particularly, the effects of sodium carboxymethylcellulose (CMC), an SEC, on the solubility of Brimonidine tartrate at various pH conditions were determined. The various concentrations of CMC tested with Brimonidine tartrate were 0%, 0.056%, 0.17%, 0.5%, 1.5% (w/v), Table III.

The samples tested also contained isotonic components, buffer components, and stabilized chlorine dioxide (Purite™), Table III. Sodium carboxymethyl-cellulose, sodium chloride, potassium chloride, calcium chloride

dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

TABLE III

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	
Brimonidine tartrate	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
CMC	0.0%	0.056%	0.17%	0.5%	1.5%	(w/v)
Stabilized chlorine dioxide[a]	0.005%	0.005%	0.005%	0.005%	0.005%	(w/v)
Sodium chloride	0.58%	0.58%	0.58%	0.58%	0.58%	(w/v)
Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)
Calcium chloride, dihydrate	0.02%	0.02%	0.02%	0.02%	0.02%	(w/v)
magnesium chloride, hexahydrate	0.006%	0.006%	0.006%	0.006%	0.006%	(w/v)
boric acid	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
sodium tetraborate, decahydrate	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)

[a]Sold under the trademark Purite ™ by Allergan, Inc.

Each sample (1 through 5) was subjected to a range of pH's from about 7 to about 10. The vials containing the sample solutions were placed on a laboratory rotator and left for equilibration for fifteen days at room temperature (~21° C.). The sample solutions were filtered using a 25 mm diameter polysulfone cellulose acetate syringe type filter with 0.45 μm pore size. The filtered solutions were assayed for Brimonidine.

Conventional HPLC and detection techniques were used to detect and determine the concentrations of soluble Brimonidine tartrate. Table IV. The solubility is plotted against pH for each CMC concentration. The experimental data points were fitted to a modified Henderson-Hasselbalch equation using a nonlinear least squares routine (Deltagraph version 4.0 DeltaPoint, Inc.), FIG. **1**. The R^2 values show the goodness of fit between the experimental values and the theoretical equation to be better than 0.991.

TABLE IV

	Solubility of Brimonidine tartrate (%)				
	0% CMC	0.056% CMC	0.17% CMC	0.5% CMC	1.5% CMC
pH					
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
7.56				0.1451	
7.68	0.0786				
7.77		0.0721			
7.81			0.0735		
8.10					0.0498
8.46				0.0313	
8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

FIG. **1** clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.0560% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.50%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

EXAMPLE 3

Brimonidine Tartrate Dimers

Brimonidine tartrate is added to a test tube containing a composition including chlorite. The test tube was allowed to equilibrate for ten days. Samples obtained from the test tube is analyzed. It is observed that a portion of the Brimonidine tartrate monomer units conjugated to form dimers.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

What is claimed is:

1. A therapeutically effective ophthalmic composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

a solubility enhancing component other than a cyclodextrin in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relataive to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

2. The composition of claim **1** wherein the alpha-2-adrenergic component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof, and mixtures thereof.

3. The composition of claim **1** wherein the therapeutically active component includes a quinoxaline component.

4. The composition of claim **3** wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.

5. The composition of claim **1** wherein said solubility enhancing component comprises an anionic polymer.

6. The composition of claim **1** wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic ago

nist component relative to the solubility in a biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

7. The composition of claim **6** wherein the solubility enhancing component comprises an anionic polymer.

8. The composition of claim **3** wherein said solubility enhancing component comprisers an anionic polymer.

9. The composition of claim **1** which further comprises an effective amount of a preservative.

10. The composition of claim **6** which further comprises an effective amount of a preservative.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

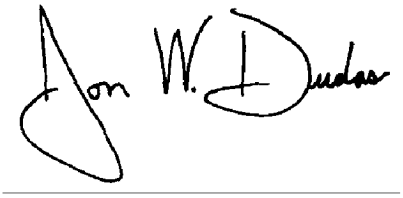
PATENT NO. : 6,673,337 B2
DATED : January 6, 2004
INVENTOR(S) : Olejnik et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16,
Line 15, delete "0.0560" and insert in place thereof -- 0.056 --
Line 16, delete "0.50" and insert in place thereof -- 0.5 --

Signed and Sealed this

Sixteenth Day of March, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

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(12) United States Patent

Olejnik et al.

(10) Patent No.: US 6,562,873 B2
(45) Date of Patent: *May 13, 2003

(54) **COMPOSITIONS CONTAINING THERAPEUTICALLY ACTIVE COMPONENTS HAVING ENHANCED SOLUBILITY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(58) **Field of Search** 514/772.4, 772.6; 424/400

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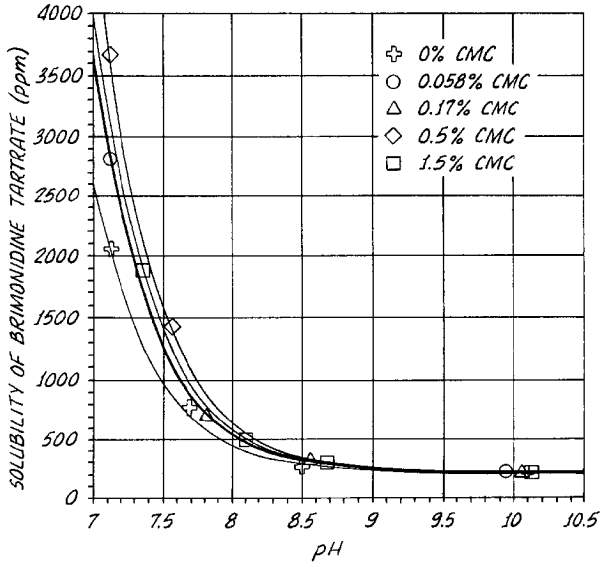
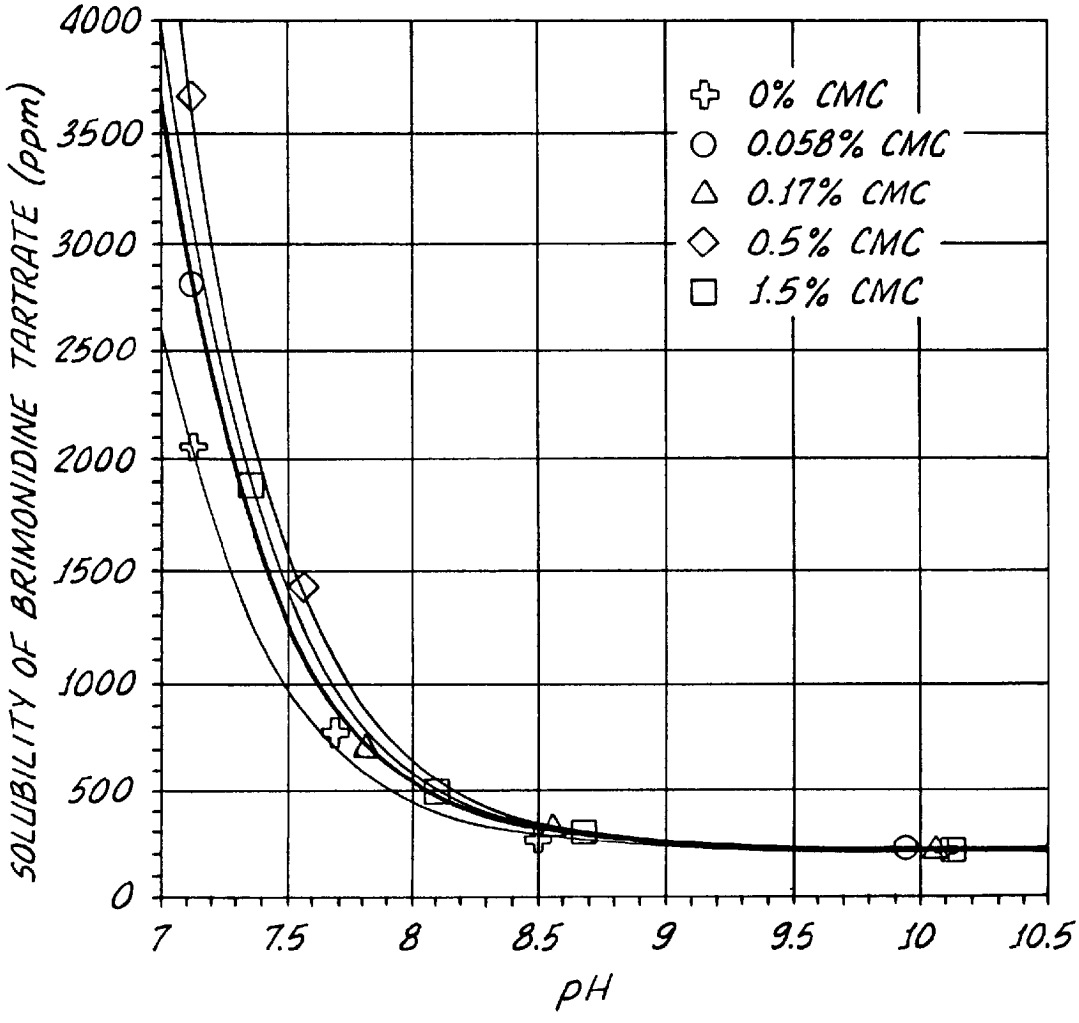
(57) **ABSTRACT**

Compositions which include therapeutically active components, solubility enhancing components other than cyclodextrins, and oxy-chloro components, wherein the oxy-chloro components are substantially effective as preservatives. In one embodiment, the oxy-chloro components are useful for preserving the therapeutically active components. In one embodiment, the oxy-chloro components include chlorite components. In a useful embodiment, the solubility enhancing components include carboxymethylcellulose.

49 Claims, 1 Drawing Sheet




SOLUBILITY OF BRIMONIDINE TARTRATE (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0
7
7.5
8
8.5
9
9.5
10
10.5
pH
0% CMC
0.058% CMC
0.17% CMC
0.5% CMC
1.5% CMC

COMPOSITIONS CONTAINING THERAPEUTICALLY ACTIVE COMPONENTS HAVING ENHANCED SOLUBILITY

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/218,206 filed Jul. 14, 2000.

BACKGROUND OF THE INVENTION

The present invention relates to compositions containing therapeutically active components having enhanced solubility. More particularly, the invention relates to compositions which include therapeutically active components (TACs) and components effective to enhance the solubility of the TACs at therapeutically effective concentrations.

TACs in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration. Additionally, the dispensed or administered TACs should be soluble in the biological system or environment into which they are administered, for example, for effective or enhanced in vivo diffusion through cell membranes or lipid bilayers. Furthermore, solubilized TACs provide other benefits, for example, reduced irritation to tissues that interact with TACs.

It is sometimes necessary to include solubilizing agents in the compositions to solubilize the TACs. However, the inclusion of solubilizing agents may reduce the effectiveness of the preservatives in the compositions.

For example, cyclodextrins are widely known in the literature to increase the solubility of poorly water soluble therapeutically active components. However, typical preservatives are rendered relatively ineffective by cyclodextrins at normal concentrations in these compositions.

There continues to be a need to provide new compositions containing TACs.

BRIEF SUMMARY OF THE INVENTION

New TAC-containing compositions have been discovered. The present compositions provide for enhanced TAC solubility substantially without detrimentally affecting the effectiveness of the preservative or preservatives being employed. Solubility enhancing components (SECs) have been found which very effectively increase the solubility of the TACs in the present compositions, and preferably in the biological systems or environments into which the components are introduced. Also, preferably, such solubilization allows the provision of more reliable and reproducible dosage forms of the drugs. This solubility enhancement in accordance with the present invention is achieved substantially without degrading preservative effectiveness. In addition, TAC-containing compositions have been discovered which include preservatives which provide substantial advantages, for example, reduced adverse interactions with the TACs and/or with the patients to whom the compositions are administered, while maintaining preservative effectiveness.

The present compositions include oxy-chloro components which are effective in at least assisting in preserving the compositions without detrimentally affecting the TACs and substantially without being detrimentally affected by the SECs. Moreover, the present oxy-chloro components provide preservative action with reduced or even substantially

no harm or irritation to the tissues to which the present compositions are administered.

The present SECs preferably are effective in solubilizing the TACs in the environment to which they are introduced, for example, a biological environment. Such solubilization preferably facilitates the advantageous transport of TACs across lipid membranes.

Soluble TACs for use in the present compositions include those components, e.g., compounds, mixtures of compounds, mixtures of other materials, useful to provide a therapeutic benefit or effect when administered to a patient, e.g. a human patient. The TACs useful in this invention include, without limitation, antibacterials, antihistamines, decongestants, antiinflammatories, antiparasitics, miotics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, muscle relaxants, diagnostics and the like and mixtures thereof. Specific examples of such TACs are conventional and well known in the art.

In one embodiment, the TACs include adrenergic agonists, precursors thereof, metabolites thereof and combinations thereof. Preferably, the TACs include alpha-2-adrenergic agonists, for example, imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. In one embodiment, the TACs include quinoxlaine components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Preferably, the quinoxaline components, including the quinoxaline derivatives, are alpha-2-adrenergic agonists. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and biologically compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is referred to as "Brimonidine tartrate."

In a useful embodiment, the SEC is other than cyclodextrin and includes a polyanionic component. As used herein, the term "polyanionic component" refers to a chemical entity, for example, an ionically charged species, such as an ionically charged polymeric material, which includes more than one discrete anionic charge, that is multiple discrete anionic charges. Preferably, the polyanionic component is selected from polymeric materials having multiple anionic charges and mixtures thereof.

Particularly useful polyanionic components are selected from anionic polymers derived from acrylic acid (meaning to include polymers from acrylic acid, acrylates and the like and mixtures thereof), anionic polymers derived from methacrylic acid (meaning to include polymers from methacrylic acid, methacrylates, and the like and mixtures thereof), anionic polymers derived from alginic acid (meaning to include alginic acid, alginates, and the like and mixtures thereof), anionic polymers of amino acids (meaning to include polymers of amino acids, amino acid salts, and the like and mixtures thereof), and the like and mixtures thereof. Very useful polyanionic components are those selected from anionic cellulose derivatives and mixtures thereof, especially carboxymethylcelluloses.

The polyanionic component preferably is sufficiently anionic to interact with or otherwise affect, in particular increase, the solubility of the TAC. This interaction preferably is sufficient to render the TAC substantially completely soluble at therapeutically effective concentrations. The amount of SEC in the composition preferably is in the range of about 0.1% (w/v) to about 30% (w/v), more preferably about 0.2% (w/v) to about 10% (w/v), and even more preferably about 0.2% (w/v) to about 0.6% (w/v).

The oxy-chloro components included in the present compositions are effective to at least assist in preserving the compositions. Any suitable oxy-chloro component effective to at least assist in preserving the compositions may be employed. Such oxy-chloro components include, without limitation, hypochlorite components, perchlorate components, chlorite components and the like and mixtures thereof.

In one useful embodiment, the oxy-chloro component includes a chlorite component. Preferably, the chlorite component includes stabilized chlorine dioxides, alkali metal chlorites and the like and mixtures thereof. Chlorite components are very effective in the present compositions and provide preservative effectiveness, often at a relatively reduced concentration, with little or no detrimental effect on the tissue to which the composition is administered. In addition, the oxy-chloro components, e.g., the chlorite components, substantially maintain preservative effectiveness in the presence of the SECs, for example, the polyanionic components. Without wishing to limit the invention to any particular theory or mechanism of operation, it is believed that such oxy-chloro components are substantially free in the presence of the SECs or do not substantially interact the SECs.

The oxy-chloro components may be effective in the compositions in the amount of less than about 1% (w/v) or about 0.8% (w/v). In a useful embodiment, the oxy-chloro components may be in the compositions in the range of about 500 ppm (w/v) or less, preferably about 10 ppm (w/v) to about 200 ppm (w/v).

In one embodiment, additional preservatives other than the oxy-chloro components are used in the compositions. Any suitable additional preservative component may be employed in accordance with the present invention, provided that it is compatible with the oxy-chloro component, the TAC and the SEC. Preservative components which are well known and/or conventionally used in the pharmaceutical field may be employed. Examples include, without limitation, sorbic acids, benzalkonium chlorides, chlorbutols and alkyl esters of p-hydroxybenzoic acids and the like and mixtures thereof. If additional preservative component is included, it preferably is present in an amount, together with the oxy-chloro component, to effectively preserve the composition.

The compositions include a liquid carrier component, for example, an aqueous liquid carrier component. Preferably, the compositions have pH's of about 7 or greater, more preferably about 7 to about 9.

In one broad aspect of the present invention, compositions are provided which comprise a TAC, a SEC, a chlorite component and an aqueous liquid carrier. Preferably the TAC is Brimonidine tartrate. The SEC is preferably an anionic cellulose derivative, more preferably a carboxymethylcellulose, for example, in an amount in the range of about 0.2% to about 0.6% (w/v).

In another broad aspect of the present invention, compositions are provided which comprise a Brimonidine tartrate, a SEC, a chlorite component and an aqueous liquid carrier component. The Brimonidine tartrate is present in an amount effective to provide a desired effect to a human or an animal after the composition is administered to the human or animal, and the SEC is preferably a carboxymethylcellulose.

In another broad aspect of the present invention, compositions are provided which comprise a TAC and a preservative component in an effective amount to at least aid in preserving the compositions. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which are biologically acceptable, chemically stable and do not substantially or significantly detrimentally affect the TACs in the compositions or the patients to whom the compositions are administered. Such compositions preferably are substantially free of cyclodextrin.

The present compositions preferably are ophthalmically acceptable, e.g. the compositions do not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art.

Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** is a graph of soluble Brimonidine tartrate verses pH at various carboxymethylcellulose concentrations.

DETAILED DESCRIPTION OF THE INVENTION

Compositions comprising TACs, SECs and oxy-chloro components are provided. The TACs in the present compositions are made more soluble and may be more effectively utilized as therapeutic agents. Suitable SECs for solubilizing TACs may be used concurrently with oxy-chloro components in the present compositions to increase the solubility of the TACs substantially without detrimentally affecting the preservative effectiveness of the oxy-chloro components. In other words, SECs employed in the present compositions may effectively increase the solubility of TACs without substantially interfering with the functions of other components in the compositions. The SECs employed in the present compositions may be effective in the solubilization of ionized TACs, unionized TACs or both.

Oxy-chloro components are included in the present compositions to assist in preserving the compositions. Particularly, the oxy-chloro components are not substantially detrimentally affected by the SECs present in the compositions. Moreover, the oxy-chloro components in the compositions are effective substantially without causing undue harm or irritation to the tissue to which the present compositions are administered.

The present compositions may, and preferably do, include liquid carrier components. For example, the components often have the characteristics of a liquid, for example, a liquid solution.

The presently useful TACs preferably are chosen to benefit from the presence of the SECs and the oxy-chloro components. In general, the TACs are provided with

increased apparent solubility, preferably increased apparent water solubility, by the presence of the SECs.

Preferably, the TACs have increased solubility in the present compositions at pH's greater than 7, as compared to identical TACs, at comparable concentrations in similar compositions, without the SECs. More preferably, the TACs have increased solubility in the present compositions at pH's in the range of about 7 to about 10, as compared to TACs in similar compositions, at comparable concentrations, without the SECs.

Without wishing to be limited by any theory or mechanism of operation, it is believed that solubilized TACs are better able to cross the lipid membranes relative to unsolubilized TACs. It is further believed that the solubilized TACs are physically smaller and are therefore more able to physically permeate or diffuse through the lipid membranes.

In one embodiment, the SECs of this invention are capable of solubilizing the TACs in the environments into which they are introduced at therapeutically effective concentrations. Preferably, the biological environments into which the present compositions are introduced have pH's ranging from about 7 to about 9. For example, a composition comprising a SEC and a TAC may be administered to the cornea of a human eye, which has a pH of about 7, wherein the TAC is substantially solubilized at the administered area. Furthermore, in one embodiment, the TACs solubilized by SECs at the administered area diffuse through biological lipid membranes more readily than TACs which are not solubilized by SECs. The solubilization of TACs preferably reduces irritation to sensitive tissues in contact or interacting with the TACs.

Examples of the therapeutically active components which may be included in the present compositions include, but are not limited to, antibacterial substances such as beta-lactam antibiotics, such as cefoxitin, n-formamidoylthienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin, cefazolin, cephaloridine, chibrorifamycin, gramicidin, bacitracin and sulfonamides; aminoglycoside antibiotics such as gentamycin, kanamycin, amikacin, sisomicin and tobramycin; nalidixic acid and its analogs such as norfloxacin and the antimicrobial combination fluoroalanine/pentizidone, nitrofurazones and analogs thereof; antihistaminics and decongestants such as pyrilamine, chlorpheniramine, tetrahydrazoline, antazoline and analogs thereof; mast-cell inhibitors of histamine release, such as cromolyn; anti-inflammatories such as cortisone, hydrocortisone, hydrocortisone acetate, betamethasone, dexamethasone, dexamethasone sodium phosphate, prednisone, methylprednisolone, medrysone, fluorometholone, prednisolone, prednisolone sodium phosphate, triamcinolone, indainethacin, sulindac, its salts and its corresponding sulfides, and analogs thereof; miotics and anticholinergics such as echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, dipivaloylepinephrine, neostigmine echothiopate iodide, demecarim bromide, carbamoyl choline chloride, methacholine, bethanechol, and analogs thereof; mydriatics such as atrophine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium, eucatropine; and the like and mixtures thereof.

Other TACs are: antiglaucama drugs, for example, timalol, and especially its maleic salt and R-timolol and a combination of timolol or R-timolol with pilocarpine; other adrenergic agonists and/or antagonists such as epinephrine and an epinephrine complex, or prodrugs such as bitartrate, borate, hydrochloride and dipivefrine derivatives; carbonic anhydrase inhibitors such as acetazolamide, dichlorphenamide, 2-(p-hydroxyphenyl)-thiothiophenesulfonamide, 6-hydroxy-2-benzothiazolesulfonamide, and 6-pivaloyloxy-2-benzothiazolesulfonamide; antiparasitic compounds and/or anti-protozoal compounds such as ivermectin, pyrimethamine, trisulfapidimidine, clindamycin and corticosteroid preparations; compounds having antiviral activity such as acyclovir, 5-iodo-2'-deoxyuridine (IDU), adenosine arabinoside (Ara-A), trifluorothymidine, interferon, and interferon-inducing agents such as poly I:C; antifungal agents such as amphotericin B, nystatin, flucytosine, natamycin and miconazole; anesthetic agents such as etidocaine cocaine, benoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine, mepivacaine and prilocaine; ophthalmic diagnostic agents, such as: (a) those used to examine the retina such as sodium fluorescein, (b) those used to examine the conjunctiva, cornea and lacrimal apparatus, such as fluorescein and rose bengal and (c) those used to examine abnormal pupillary responses such as methacholine, cocaine, adrenaline, atropine, hydroxyamphetamine and pilocarpine; ophthalmic agents used as adjuncts in surgery, such as alpha-chymotrypsin and hyaluronidase; chelating agents such as ethylenediaminetetraacetic acid (EDTA) and deferoxamine; immunosuppressants and anti-metabolites such as methotrexate, cyclophosphamide, 6-mercaptopurine and azathioprine and combinations of the compounds mentioned above, such as antibiotics/antiinflammatories combinations such as the combination of neomycin sulfate and dexamethasone sodium phosphate and combinations concomitantly used for treating glaucoma, for example, a combination of timolol maleate and aceclidine; and the like and mixtures thereof.

In a preferred embodiment, the useful TACs include adrenergic agonists. The adrenergic agonists preferably are molecules containing amines. Also, the adrenergic agonists preferably are amine-containing molecules with pKa's of greater than 7, preferably about 7 to about 9.

More preferably, the useful TACs include alpha-adrenergic agonists. Examples of alpha-adrengergic agonists include, but not limited to, adrafinil, adrenolone, amidephrine, apraclonidine, budralazine, clonidine, cyclopentamine, detomidine, dimetofrine, dipivefrin, ephedrine, epinephrine, fenoxazoline, guanabenz, guanfacine, hydroxyamphetamine, ibopamine, indanazoline, isometheptene, mephentermine, metaraminol, methoxamine, methylhexaneamine, metizolene, midodrine, naphazoline, norepinephrine, norfenefrine, octodrine, octopamine, oxymetazoline, phenylephrine, phenylpropanolamine, phenylpropylmethylamine, pholedrine, propylhexedrine, pseudoephedrine, rilmenidine, synephrine, tetrahydrozoline, tiamenidine, tramazoline, tuaminoheptane, tymazoline, tyramine, xylometazoline, and the like and mixtures thereof.

In a still more preferred embodiment, the useful TACs include alpha-2-adrenergic agonists. As used herein, the term "alpha-2 adrenergic agonist" includes chemical entities, such as compounds, ions, complexes and the like, that produces a net sympatholytic response, resulting in increased accommodation, for example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or, for example, to postsynaptic alpha-2

receptors on smooth muscle cells. A sympatholytic response is characterized by the inhibition, diminishment, or prevention of the effects of impulses conveyed by the sympathetic nervous system. The alpha-2 adrenergic agonists of the invention bind to the alpha-2 adrenergic receptors presynaptically, causing negative feedback to decrease the release of neuronal norepinephrine. Additionally, they also work on alpha-2 adrenergic receptors postsynaptically, inhibiting beta-adrenergic receptor-stimulated formation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2 adrenergic receptors on other intracellular pathways. Activity at either pre- or postsynaptic alpha-2 adrenergic receptors will result in a decreased adrenergic influence. Decreased adrenergic influence results in increased contraction resulting from cholinergic innervations. Alpha-2 adrenergic agonists also include compounds that have neuroprotective activity. For example, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is an alpha-2-adrenergic agonist which has a neuroprotective activity through an unknown mechanism.

Without limiting the invention to the specific groups and compounds listed, the following is a list of representative alpha-2 adrenergic agonists useful in this invention: imino-imidazolines, including clonidine, apraclonidine; imidazolines, including naphazoline, xymetazoline, tetrahydrozoline, and tramazoline; imidazoles, including detomidine, medetomidine, and dexmedetomidine; azepines, including B-HT 920 (6-allyl-2-amino-5,6,7,8 tetrahydro-4H-thiazolo[4,5-d]-azepine and B-HT 933; thiazines, including xylazine; oxazolines, including rilmenidine; guanidines, including guanabenz and guanfacine; catecholamines and the like.

Particularly useful alpha-2-adrenergic agonists include quinoxaline components. In one embodiment, the quinoxaline components include quinoxaline, derivatives thereof and mixtures thereof. Preferably, the derivatives of quinoxaline include (2-imidozolin-2-ylamino) quinoxaline. More preferably, the derivatives of quinoxaline include 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline. The "halide" of the 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline may be a fluorine, a chlorine, an iodine, or preferably, a bromine, to form 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Even more preferably, the derivatives of quinoxaline to be used in accordance with this invention include a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, or Brimonidine tartrate.

Other useful quinoxaline derivatives are well known. For example, useful derivatives of a quinoxaline include the ones disclose by Burke et al U.S. Pat. No. 5,703,077. See also Danielwicz et al 3,890,319. Each of the disclosures of Burke et al and Danielwicz et al is incorporated in its entirety by reference herein.

The quinoxaline and derivatives thereof, for example Brimonidine tartrate, are amine-containing and preferably have pKa's of greater than 7, preferably about 7.5 to 9.

Analogs of the foregoing compounds that function as alpha-2 adrenergic agonists also are specifically intended to be embraced by the invention.

Preferably, the alpha-2-adrenergic agonists, for example the ones listed above, are effective toward activating one or more of alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and alpha-2D-adrenergic receptors.

Other useful TACs include ocular hypotensive agents (Woodward et al U.S. Pat. No. 5,688,819), cyclosporins (Ding et al U.S. Pat. No. 5,474,979), androgen tears (Sullivan U.S. Pat. No. 5,620,921), pyranoquinolinone derivatives (Cairns et al U.S. Pat. No. 4,474,787), compounds having retinoid-like activities (Chandraratna U.S. Pat. No. 5,089,509), ketorolac/pyrrole-1-carboxylic acids (Muchowski et al U.S. Pat. No. 4,089,969), ofloxacins/benzoxazine derivatives (Hayakawa et al U.S. Pat. No. 4,382,892), memantines (Lipton et al U.S. Pat. No. 5,922,773), RAR antagonists (Klein et al U.S. Pat. No. 5,952,345), RAR-alpha agonists (Teng et al U.S. Pat. No. 5,856,490). Each of the disclosures referred to in the above patents is incorporated in its entirety herein by reference.

In one embodiment, the TACs, for example Brimonidine tartrate, are substantially unionized in the composition. In another embodiment, the TACs are substantially unionized in the environment to which they are administered, for example the cornea of the human eye. Without wishing to be limited by any theory or mechanism of action, it is believed that the unionized forms of the TACs facilitate their permeation across membrane lipid bilayers.

Any suitable SEC, other than cyclodextrin, may be employed in accordance with the present invention. In one embodiment, the SECs include pyrrolinidone components. Examples of pyrrolinidone components are polyvinylpyrrolinidones, derivatives thereof and mixtures thereof. In a preferred embodiment, the SECs include polyanionic components. The useful polyanionic components include, but are not limited to, those materials which are effective in increasing the apparent solubility, preferably water solubility, of poorly soluble TACs and/or enhance the stability of the TACs and/or reduce unwanted side effects of the TACs. Furthermore, the polyanionic component is preferably ophthalmically acceptable at the concentrations used. Additionally, the polyanionic component preferably includes three (3) or more anionic (or negative) charges. In the event that the polyanionic component is a polymeric material, it is preferred that each of the repeating units of the polymeric material include a discrete anionic charge. Particularly useful anionic components are those which are water soluble, for example, soluble at the concentrations used in the presently useful liquid aqueous media, such as a liquid aqueous medium containing the polyanionic component and chlorite component.

The polyanionic component is preferably sufficiently anionic to interact with the TAC. Such interaction is believed to be desirable to solubilize the TAC and/or to maintain such TAC soluble in the carrier component, for example a liquid medium.

Polyanionic components also include one or more polymeric materials having multiple anionic charges. Examples include:

- metal carboxymethylstarchs
- metal carboxymethylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - metal acrylates and methacrylates
  - alginic acid
  - metal alginates
  - vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - p-styrenesulfonic acid
  - metal p-styrenesulfonate
  - 2-methacryloyloxyethylsulfonic acids

metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

In one embodiment, the polyanionic components include anionic polysaccharides, other than cyclodextrins, which tend to exist in ionized forms at higher pH's, for example, pH's of about 7 or higher. The following are some examples of anionic polysaccharides which may be employed in accordance with this invention.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose.

Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks.

Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of which can be sulfated or nonsulfated, joined by alternating 1–3 and beta 1–4 glycosidic linkages. Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss.

Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water.

Other polysaccharides found useful in the present invention are hydrophilic colloidal materials and include the natural gums such as gellan gum, alginate gums, i.e., the ammonium and alkali metal salts of alginic acid and mixtures thereof. In addition, chitosan, which is the common name for deacetylated chitin is useful. Chitin is a natural product comprising poly-(N-acetyl-D-glucosamine). Gellan gum is produced from the fermentation of pseudomonas elodea to yield an extracellular heteropolysaccharide. The alginates and chitosan are available as dry powders from Protan, Inc., Commack, N.Y. Gellan gum is available from the Kelco Division of Merk & Co., Inc., San Diego, Calif.

Generally, the alginates can be any of the water-soluble alginates including the alkali metal alginates, such as sodium, potassium, lithium, rubidium and cesium salts of alginic acid, as well as the ammonium salt, and the soluble alginates of an organic base such as mono-, di-, or triethanolamine alginates, aniline alginates, and the like. Generally, about 0.2% to about 1% by weight and, preferably, about 0.5% to about 3.0% by weight of gellan, alginate or chitosan ionic polysaccharides, based upon the total weight of the composition, are used to obtain the gel compositions of the invention.

A particularly useful class of polyanionic component includes anionic cellulose derivatives. Anionic cellulose derivatives include metal carboxymethylcelluloses, metal carboxymethylhydroxyethylcelluloses and hydroxypropylmethylcelluloses and derivatives thereof.

The present polyanionic components often can exist in the unionized state, for example, in the solid state, in combination with a companion or counter ion, in particular a plurality of discrete cations equal in number to the number of discrete anionic charges so that the unionized polyanionic component is electrically neutral. For example, the present unionized polyanionic components may be present in the acid form and/or in combination with one or more metals. Since the polyanionic components are preferably ophthalmically acceptable, it is preferred that the metal associated with the unionized polyanionic component be ophthalmically acceptable in the concentrations used. Particularly useful metals include the alkali metals, for example, sodium and potassium, the alkaline earth metals, for example, calcium and magnesium, and mixtures thereof. Sodium is very useful to provide the counter ion in the unionized polyanionic component. Polyanionic components which, in the unionized states, are combined with cations other than H+and metal cations can be employed in the present invention.

In a preferred embodiment, the polyanionic polymers are cyclized. More preferably, the cyclized anionic polymers include less than ten monomer units. Even more preferably, the cyclized polyanionic polymers include less than six monomer units.

The amount of SEC in the present compositions is not of critical importance so long as solubility at the alpha-2-adrenergic agonist component is at least somewhat increased and is present in a biologically acceptable amount. Such amount should be effective to perform the desired function or functions in the present composition and/or after administration to the human or animal. In one embodiment, the amount of SEC, preferably the polyanionic component, is sufficient to complex at least in a major amount, and more preferably substantially all, of the TAC in the present composition. In one useful embodiment, the amount of polyanionic component in the present composition is in the range of about 0.1% to about 30% (w/v) or more of the composition. Preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 10% (w/v). More preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 0.6% (w/v). Even more preferably, the polyanionic component is carboxymethylcellulose and is present in the composition in the range of about 0.2% (w/v) to about 0.6% (w/v). A particularly useful concentration of carboxymethylcellulose in the present composition is about 0.5%.

In one embodiment, carboxymethylcellulose may help solubilize ionized TACs. In another embodiment, carboxymethylcellulose may help solubilize unionized TACs. In a preferred embodiment, the carboxylmethylcellulose help solubilize ionized Brimonidine tartrate. More preferably, the carboxylmethylcellulose helps solubilize unionized Brimonidine tartrate.

In one broad embodiment, the preservative components are selected so as to be effective and efficacious as preservatives in the present compositions, that is in the presence of SECs, and preferably have reduced toxicity and more preferably substantially no toxicity when the compositions are administered to a human or animal.

Preservatives which are commonly used in pharmaceutical compositions are often less effective when used in the presence of solubilizing agents. In certain instances, this reduced preservative efficacy can be compensated for by using increased amounts of the preservative. However, where sensitive or delicate body tissue is involved, this approach may not be available since the preservative itself may cause some adverse reaction or sensitivity in the human or animal, to whom the composition is administered.

Preferably, the present preservative components or components effective in aiding to preserve the compositions are effective in concentrations of less than about 1% (w/v) or about 0.8% (w/v) and may be 500 ppm (w/v) or less, for example, in the range of about 10 ppm (w/v) or less to about 200 ppm (w/v). Preservative components or components effective in aiding to preserve the compositions in accor-

dance with the present invention preferably include, but are not limited to, those which form complexes with the polyanionic component to a lesser extent than does benzalkonium chloride.

Examples of the components effective in aiding to preserve the compositions, preferably the TACs therein, include, but are not limited to, oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof. Specific examples of oxy-chloro components useful as preservatives in accordance with the present invention include hypochlorite components, for example hypochlorites; chlorate components, for example chlorates; perchlorate components, for example perchlorates; and chlorite components. Examples of chlorite components include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures therefor. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Purite® by Allergan, Inc. Other examples of oxidative preservative components includes peroxy components. For example, trace amounts of peroxy components stabilized with a hydrogen peroxide stabilizer, such as diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1, 1-diphosphonic acid, may be utilized as a preservative for use in components designed to be used in the ocular environment. Also, virtually any peroxy component may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. Examples of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, may not be stabilized utilizing the present system. See, for example, Martin et al U.S. Pat. No. 5,725,887, the disclosure of which is incorporated in its entirety herein by reference.

In a broad embodiment of the invention, additional preservatives other than oxidative preservative components may be included in the compositions. The choice of preservatives may depend on the route of administration. Preservatives suitable for compositions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic compositions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds and the like known generically as "benzalkonium chloride." For compositions to be administered by inhalation, however, the preferred preservative is chlorbutol and the like. Other preservatives which may be used, especially for compositions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and the like and mixtures thereof, such as the mixture of methyl, ethyl, propyl and butyl esters which is sold under the trade name "Nipastat."

In another broad aspect of the present invention, compositions are provided which comprise a TAC, a preservative component in an effective amount to at least aid in preserving, preferably in an amount effective to preserve, the compositions and a liquid carrier component. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which (1) do not substantially or significantly detrimentally affect the TACs in the compositions or the patients to whom the compositions are administered, and (2) are substantially biologically acceptable and chemically stable. Such compositions in accordance with the present invention comprise a TAC, an oxy-chloro component, and a liquid carrier component, and preferably are substantially free of cyclodextrins.

The carrier components useful in the present invention are selected to be non-toxic and have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. In one embodiment, the carrier component is a liquid carrier. In a preferred embodiment, the carrier component is a liquid aqueous carrier component. A particularly useful aqueous liquid carrier component is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution. The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5. The liquid medium preferably has an ophthalmically acceptable tonicity level, for example, of at least about 200 mOsmol/kg, more preferably in the range of about 200 to about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the carrier components substantially correspond to the tonicity of the fluids of the eye, in particular the human eye.

In one embodiment, the carrier components containing the TACs, SECs and preservatives may have viscosities of more than about 0.01 centipoise (cps) at 25° C., preferably more than about 1 cps, even more preferably more than about 10 cps at 25° C. In a preferred embodiment, the composition has a viscosity of about 50 cps at 25° C. and comprises a conventional buffer saline solution, a carboxymethylcellulose and a Brimonidine tartrate.

In order to insure that the pH of the aqueous liquid carrier component, and thus the pH of the composition, is maintained within the desired range, the aqueous liquid carrier component may include at least one buffer component. Although any suitable buffer component may be employed, it is preferred to select such component so as not to produce a significant amount of chlorine dioxide or evolve significant amounts of gas, such as CO_2. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components are advantageously used in the present invention.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid aqueous carrier component and do not have deleterious or toxic properties which could harm the human or animal to whom the present compositions are administered. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring

agents, surface active agents, thickeners, lubricants, and the like, for example, such additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gun tragacanth and gun acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof. Such aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gun tragacanth, naturally-occurring phosphatides, for example, soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Brimonidine tartrate has a pKa of about 7.78. The pH-solubility profile of 0.5% (w/v) Brimonidine tartrate in a formulation, Ophthalmic Solution, was established in the pH range of about 5 to about 8 at 23° C. Table 1. It will be understood that concentrations of adrenergic agonists other than 0.5% may be used, so long as they have therapeutic activity. Likewise, the temperature may be varied, for example, solubility curves may be performed at 37° C. (98.6° F.). The formulation vehicle was prepared by first dissolving polyvinyl alcohol (PVA) in water. The PVA was added to approximately ⅓ of the required total amount of purified water with constant stirring. The slurry was stirred for 20–30 minutes and then heated to 80–95° C. with constant stirring. The mixture was removed from the heat source within 1 hour after having reached the temperature of 80–90° C. and stirred for an additional 10 minutes to ensure homogeneity (Part I). The other ingredients of the Ophthalmic Solution, except for Brimonidine tartrate, were dissolved in a separate container with an additional ⅓ of the required total amount of purified water (Part II). The PVA mixture (Part I) was then quantitatively transferred to Part II using several rinse volumes of purified water. The solution was adjusted to final volume with purified water without pH adjustment.

Brimonidine tartrate was weighed and transferred to a 10 mL test tube containing 5 mL of the formulation vehicle described above. The pH of each sample was then adjusted to a desired value using dilute sodium hydroxide and/or dilute hydrochloric acid. The samples were placed in a rack on a stir plate and stirred at high speed to achieve uniform mixing for 2 days; a partition was placed between the rack and the stir plate to prevent any heat diffusion from the stir plate to the samples. The temperature of the laboratory was monitored throughout the study and was found to be 23±1° C.

At the end of two days of stirring, the pH value of each sample was measured, and then approximately 1 mL of each sample was placed in a micro centrifuge tube (polypropylene) and centrifuged at 4,000 rpm for 10 minutes. The supernatant was filtered through a 1 μm filter unit (Whatman, 13 mm, PTFE). The first 3–4 drops of the filtrate were discarded; the rest of the filtrate was received and diluted quantitatively with HPLC mobile phase. The dilute sample was then injected directly on the HPLC column (Dupont Zorbax, 250 mm×4.6 mm, 5μm) for Brimonidine tartrate assay in order to quantify the amount of Brimonidine tartrate. A control of 10.05% Brimonidine tartrate was prepared in the formulation vehicle at pH 6.3–6.5 and assayed before (untreated) and after (treated) centrifugation and filtration. This was done to evaluate the potential loss of Brimonidine tartrate in these two steps of the sample preparation. To ensure reproducibility, the study was repeated on consecutive days.

TABLE I

0.5% Brimonidine tartrate in Ophthalmic Solution.

Ingredient	Percent (w/v)
Brimonidine tartrate	0.50
Benzalkonium Chloride, NF	0.0050
Polyvinyl Alcohol, USP	1.4
Sodium Chloride, USP	0.66
Sodium Citrate, Dihydrate, USP	0.45
Hydrochloric Acid, NF or Sodium Hydroxide, NF for pH adjustment	5–8
Purified Water, USP	QS

The solubility data for Brimonidine tartrate in the formulation vehicles are presented in Table II. The results show that the solubility of Brimonidine tartrate is highly pH-dependent and spans more than two orders of magnitude over the pH range of 5–8. The solubility decreases sharply as the pH increases. The results for the treated and untreated controls are very close, suggesting that centrifugation and filtration does not cause any significant loss of Brimonidine

tartrate. The two solubility profiles obtained on consecutive days agree with each other.

TABLE II

Solubility of Brimonidine tartrate in the Ophthalmic Solution Over pH Range of 5 to 8.

	STUDY 1		STUDY 2	
Sample	pH[a]	Solubility[e]	pH[a]	Solubility[e]
1	5.55	≦164.4[b]	5.50	≦200.6[b]
2	5.92	132.6	5.92	160.8
3	6.14	30.4	6.06	50.1
4	6.57	7.55	6.90	3.19
5	7.00	2.69	7.40	1.19
6	7.45	1.17	7.77	0.63
7	7.83	0.62	7.86	0.58
8	—	—	7.88	0.54
Control/ (untreated)	—	0.486[c]	—	—
Control/ (treated)	—	0.484[d]	—	—

[a]Measured after stirring for two-days before sample withdrawal for centrifugation and filtration.
[b]Represents theoretical concentration based on sample weight. The sample solution was clear indicating that all of the Brimonidine tartrate had dissolved.
[c]Concentration of Brimonidine tartrate in control before centrifugation and filtration step.
[d]Concentration of Brimonidine tartrate in control after centrifugation and filtration step.
[e]% w/v.

EXAMPLE 2

The pH-solubility profiles of Brimonidine tartrate in compositions (solutions) containing SECs and oxy-chloro components were determined. Particularly, the effects of sodium carboxymethylcellulose (CMC), an SEC, on the solubility of Brimonidine tartrate at various pH conditions were determined. The various concentrations of CMC tested with Brimonidine tartrate were 0%, 0.056%, 0.17%, 0.5%, 1.5% (w/v), Table III.

The samples tested also contained isotonic components, buffer components, and stabilized chlorine dioxide (Purite™), Table III. Sodium carboxymethyl-cellulose, sodium chloride, potassium chloride, calcium chloride dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

TABLE III

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
Brimonidine tartrate	0.2%	0.2%	0.2%	0.2%	0.2% (w/v)
CMC	0.0%	0.056%	0.17%	0.5%	1.5% (w/v)
Stabilized chlorine dioxide[a]	0.005%	0.005%	0.005%	0.005%	0.005% (w/v)
Sodium chloride	0.58%	0.58%	0.58%	0.58%	0.58% (w/v)
Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14% (w/v)
Calcium chloride, dihydrate	0.02%	0.02%	0.02%	0.02%	0.02% (w/v)
magnesium chloride, hexahydrate	0.006%	0.006%	0.006%	0.006%	0.006% (w/v)
boric acid	0.2%	0.2%	0.2%	0.2%	0.2% (w/v)
sodium tetraborate, decahydrate	0.14%	0.14%	0.14%	0.14%	0.14% (w/v)

[a]Sold under the trademark Purite ™ by Allergan, Inc.

Each sample (1 through 5) was subjected to a range of pH's from about 7 to about 10. The vials containing the sample solutions were placed on a laboratory rotator and left for equilibration for fifteen days at room temperature (~21° C.). The sample solutions were filtered using a 25 mm diameter polysulfone cellulose acetate syringe type filter with 0.45 μm pore size. The filtered solutions were assayed for Brimonidine.

Conventional HPLC and detection techniques were used to detect and determine the concentrations of soluble Brimonidine tartrate. Table IV. The solubility is plotted against pH for each CMC concentration. The experimental data points were fitted to a modified Henderson-Hasselbalch equation using a nonlinear least squares routine (Deltagraph version 4.0 DeltaPoint, Inc.), FIG. **1**. The R^2 values show the goodness of fit between the experimental values and the theoretical equation to be better than 0.991.

TABLE IV

Solubility of Brimonidine tartrate (%)

pH	0% CMC	0.056% CMC	0.17% CMC	0.5% CMC	1.5% CMC
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
7.56				0.1451	
7.68	0.0786				
7.77		0.0721			
7.81			0.0735		
8.10					0.0498
8.46				0.0313	
8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

FIG. **1** clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.056% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.5%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

While this invention has been described with respect to various specific examples and embodiments, it is to be

understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

What is claimed is:

1. A composition comprising:

a therapeutically active component selected from the group consisting of alpha-2-adrenergic agonists and mixtures thereof, and being present in an amount effective to provide a desired therapeutic benefit to a patient to whom the composition is administered;

a solubility enhancing component, other than a cyclodextrin, in an amount effective to increase the solubility of the therapeutically active component in the composition relative to the solubility of an identical therapeutically active component in a similar composition without the solubility enhancing component;

an oxy-chloro component in an effective amount to at least aid in preserving the composition; and

a liquid carrier component.

2. The composition of claim **1** wherein the therapeutically active component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, and mixtures thereof.

3. The composition of claim **1** wherein the therapeutically active component includes a quinoxaline component.

4. The composition of claim **3** wherein the quinoxaline component is selected from the group consisting of quinoxalines, quinoxaline derivatives, and mixtures thereof.

5. The composition of claim **3** wherein the quinoxaline component is selected from the group consisting of quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and mixtures thereof.

6. The composition of claim **1** wherein the therapeutically active component comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

7. The composition of claim **1** wherein the therapeutically active component has increased diffusion through a lipid membrane relative to an identical therapeutically active component in a similar composition without the solubility enhancing component.

8. The composition of claim **1** wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the therapeutically active component relative to the solubility in a biological environment of an identical therapeutically active component in a similar composition without the solubility enhancing component.

9. The composition of claim **1** wherein the solubility enhancing component comprises a polyanionic component.

10. The composition of claim **9** wherein said polyanionic components is selected from the group consisting of anionic cellulose derivatives, anionic polymers derived from acrylic acid, anionic polymers derived from methacrylic acid, anionic polymers derived from alginic acid, anionic polymers derived from amino acids and mixtures thereof.

11. The composition of claim **1** wherein the solubility enhancing component comprises an anionic cellulose derivative.

12. The composition of claim **1** wherein the solubility enhancing component comprises a carboxymethylcellulose.

13. The composition of claim **1** wherein the solubility enhancing component is present in an amount in a range of about 0.1% (w/v) to about 30% (w/v).

14. The composition of claim **1** wherein the solubility enhancing component is present in an amount in a range of about 0.2% (w/v) to about 10 (w/v).

15. The composition of claim **1** wherein the solubility enhancing component is present in an amount in a range of about 0.2% (w/v) to about 0.6% (w/v).

16. The composition of claim **1** wherein the oxy-chloro component is selected from the group consisting of hypochlorite components, perchlorate components, chlorite components and mixtures thereof.

17. The composition of claim **1** wherein the oxy-chloro component comprises a chlorite component.

18. The composition of claim **1** wherein the oxy-chloro component comprises stabilized chlorine dioxide.

19. The composition of claim **1**, wherein the oxy-chloro component is present in an amount of about 500 ppm (w/v) or less.

20. The composition of claim **1** wherein the oxy-chloro component is present in an amount in a range of about 10 ppm (w/v) to about 200 ppm (w/v).

21. The composition of claim 1 which further comprises an additional preservative component other than the oxy-chloro component in an amount effective to at least aid in preserving the composition.

22. The composition of claim **21**, wherein the additional preservative component is selected from the group consisting of sorbic acid, benzalkonium chloride, chlorbutol and alkyl esters of p-hydroxybenzoic acid and mixtures thereof.

23. The composition of claim **1** wherein the liquid carrier is an aqueous liquid carrier component.

24. The composition of claim **1** which is a solution.

25. The composition of claim 1 which has a pH of about 7 or greater.

26. The composition of claim **1** which has a pH in a range of about 7 to about 9.

27. The composition of claim **1** which is ophthalmically acceptable.

28. A composition comprising:

a therapeutically active component selected from the group consisting of alpha-2-adrenergic agonists and mixtures thereof in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

an anionic cellulose derivative in an amount effective to increase the solubility of the therapeutically active component;

a chlorite component in an effective amount to at least aid in preserving the composition; and

an aqueous liquid carrier component.

29. The composition of claim **28** wherein the therapeutically active component comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

30. The composition of claim **28** wherein the anionic cellulose derivative comprises carboxymethylcellulose.

31. The composition of claim **28** wherein the anionic cellulose derivative is present in an amount in a range of about 0.2% to about 0.6% (w/v).

32. A composition comprising:

a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

a solubility enhancing component in an amount effective to increase the solubility of the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline;

a chlorite component in an effective amount to at least aid in preserving the composition; and

an aqueous liquid carrier component.

33. The composition of claim **32** wherein the solubility enhancing component comprises a carboxymethylcellulose.

34. The composition of claim **32** which is ophthalmically acceptable.

35. A composition comprising:

a therapeutically active component in an amount effective to provide a desired therapeutic benefit to a patient to whom the composition is administered;

an oxy-chloro component in an effective amount to at least aid in preserving the composition; and

a liquid carrier component, wherein the composition is substantially free of cyclodextrins.

36. The composition of claim **35** wherein the therapeutically active component is selected from the group consisting of antibacterials, antihistamines, decongestants, antiinflammatories, antiparasitics, miotics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplascics, antihypertensives, muscle relaxants, diagnostics, and mixtures thereof.

37. The composition of claim **35** wherein the therapeutically active component is selected from the group consisting of adrenergic agonists and mixtures thereof.

38. The composition of claim **35** wherein the therapeutically active component is selected from the group consisting of alpha-2-adrenergic agonists and mixtures thereof.

39. The composition of claim **35** wherein the therapeutically active component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoleS, azepines, thiazines, oxazolines, guanidines, catecholamines, and mixtures thereof.

40. The composition of claim **35** wherein the therapeutically active component includes a quinoxaline component.

41. The composition of claim **40** wherein the quinoxaline component is selected from the group consisting of quinoxalines, quinoxaline derivatives, and mixtures thereof.

42. The composition of claim **40** wherein the quinoxaline component is selected from the group consisting of quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and mixtures thereof.

43. The composition of claim **35** wherein the therapeutically active component comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

44. The composition of claim **35**, which further includes a solubility enhancing component, other than a cyclodextrin, in an amount effective to increase the solubility of the therapeutically active component in the composition relative to the solubility of an identical therapeutically active component in a similar composition without the solubility enhancing component.

45. The composition of claim **44** wherein the solubility enhancing component comprises a polyanionic component.

46. The composition of claim **35** wherein the oxy-chloro component is selected from the group consisting of hypochlorite components, perchlorate components, chlorite components and mixtures thereof.

47. The composition of claim **35** wherein the oxy-chloro component comprises a chlorite component.

48. The composition of claim **35** wherein the oxy-chloro component comprises stabilized chlorine dioxide.

49. The composition of claim **35** which is ophthalmically acceptable.

* * * * *

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Olejnik et al.

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(54) **COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 18 days.

This patent is subject to a terminal disclaimer.

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(60) Provisional application No. 60/218,200, filed on Jul. 14, 2002.

(51) **Int. Cl.**[7] **A61K 33/14**; A61K 9/00; A61K 9/08

(52) **U.S. Cl.** **424/427**; 424/400; 424/401; 424/466; 424/422; 514/772.4; 514/772.6; 514/249

(58) **Field of Search** 424/661, 400, 424/427, 401, 422; 514/772.4, 772.6, 249

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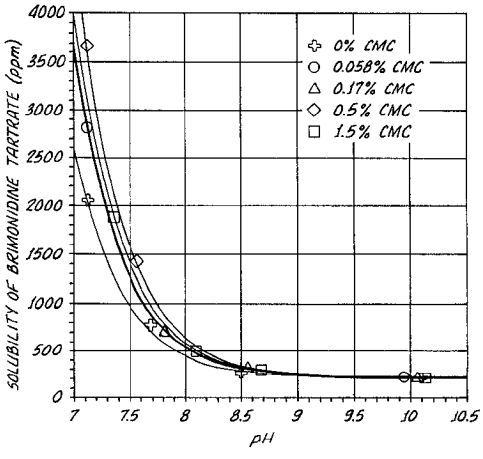
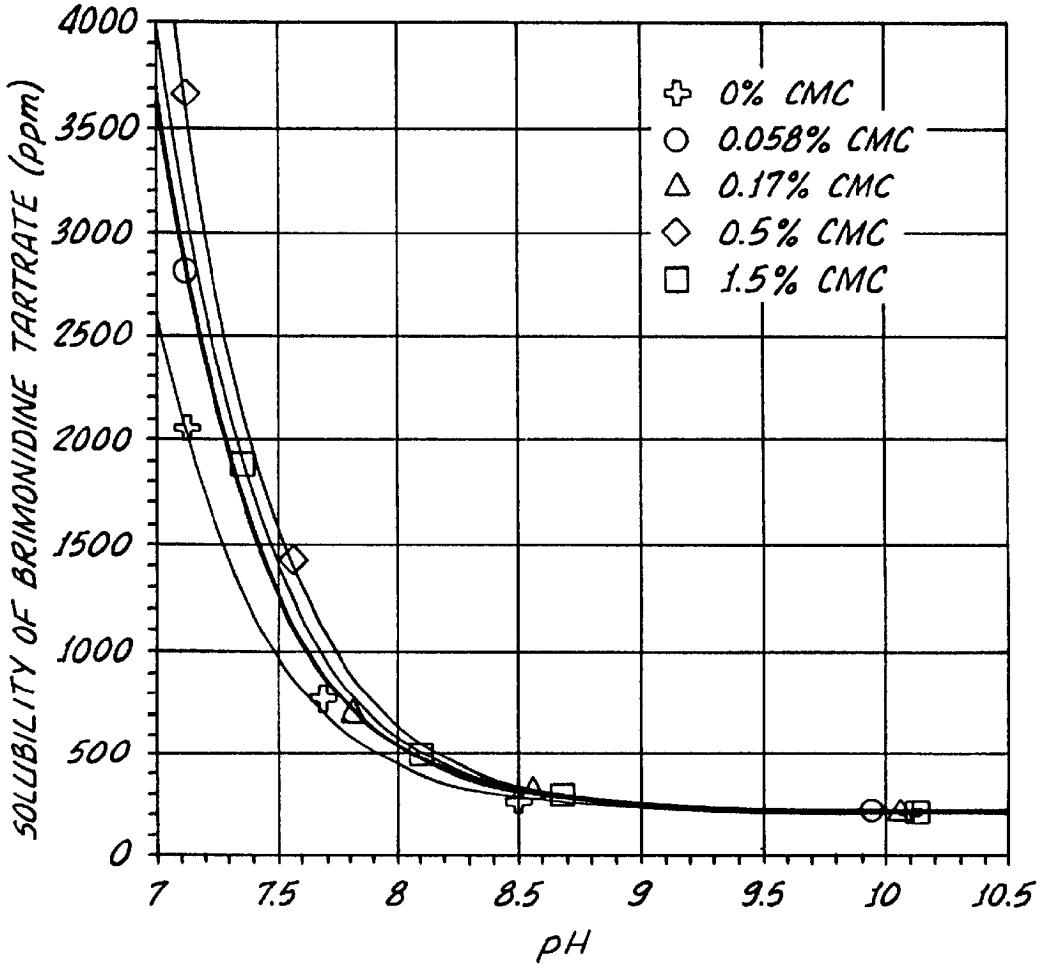
(57) **ABSTRACT**

Compositions useful for improving effectiveness of alpha-2-adrenergic agonist components include carrier components, alpha-2-adrenergic agonist components, solubility enhancing components which aid in solubilizing the alpha-2-adrenergic agonist components. In one embodiment, the alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. In another embodiment, the solubility enhancing components include carboxymethylcellulose.

22 Claims, 1 Drawing Sheet




SOLUBILITY OF BRIMONIDINE TARTRATE (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0
7
7.5
8
8.5
9
9.5
10
10.5
pH
0% CMC
0.058% CMC
0.17% CMC
0.5% CMC
1.5% CMC

COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of application Ser. No. 09/904,018, filed Jul. 10, 2001 which, in turn, claims the benefit of U.S. Provisional Application Ser. No. 60/218,200, filed Jul. 14, 2000. The disclosure of each of the above-noted applications is incorporated in its entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to compositions containing alpha-2-adrenergic agonist components. More particularly, the invention relates to such compositions in which the alpha-2-adrenergic agonist components have enhanced solubility at the therapeutically effective concentrations.

Alpha-2-adrenergic agonist components include chemical entities, such as compounds, ions, complexes and the like, which are effective to act on or bind to Alpha-2-adrenergic receptors and provide a therapeutic effect. Alpha-2-adrenergic agonist components means the agonists themselves and any and all precursors thereof, metabolites thereof and combinations thereof. One of the continuing challenges of formulating compositions having alpha-2-adrenergic agonist components is to render such components more effective. For example, alpha-2-adrenergic agonist components in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration.

Additionally, the dispensed or administered alpha-2-adrenergic agonist components should advantageously be soluble in biological systems or environments, for example, for effective or enhanced in vivo diffusion through cell membranes or lipid bilayers. Some alpha-2-adrenergic agonist components with higher pKa's, for example, greater than about 7, tend to diffuse very well through lipid membranes at pH valves near their pka, because in such circumstances they are predominantly unionized in neutral to alkaline biological environments. However, some of these alpha-2-adrenergic agonist components become insoluble at neutral to alkaline biological pH's. Such insolubility may decrease membrane diffusion capabilities, rendering the alpha-2-adrenergic agonist components less effective and/or their therapeutic effects more variable at a given dosage. Furthermore, solubilized alpha-2-adrenergic agonist components provide other benefits, for example, reduced irritation to tissues that interact with alpha-2-adrenergic agonist components.

There continues to be a need for new compositions containing alpha-2-adrenergic agonist components.

SUMMARY OF THE INVENTION

New alpha-2-adrenergic agonist component-containing compositions have been discovered. The present compositions contain certain materials which are effective in at least aiding or assisting in solubilizing the alpha-2-adrenergic agonist components in the compositions, and preferably in environments to which the compositions are administered or introduced, for example, biological environments, such as the human eye. Preferably, solubilization of the alpha-2-adrenergic agonist components in accordance with the present invention facilitates transport of such components across lipid membranes. Also, preferably such solubilization

allows the provision of more reliable and reproducible dosage forms of the drug. In addition, alpha-2-adrenergic agonist component-containing compositions have been discovered which include preservatives which provide substantial advantages, for example, reduced adverse interactions with the alpha-2-adrenergic agonist components and/or with the patients to whom the compositions are administered, while maintaining preservative effectiveness.

The present compositions preferably enhance the effectiveness of alpha-2-adrenergic agonist components by increasing the apparent water solubility of the alpha-2-adrenergic agonist components, preferably at pH's higher than neutral. The present compositions include, in addition to the adrenergic agonist components, solubility enhancing components (SECs) in amounts effective to enhance the solubility of the alpha-2-adrenergic agonist components. Preferably, the alpha-2-adrenergic agonist components are more soluble in the present compositions having, for example, pH's of about 7 or greater, relative to similar compositions without the SECs. In another embodiment, the alpha-2-adrenergic agonist components of the present compositions are more soluble in neutral, preferably alkaline, biological environments into which the compositions are administered relative to alpha-2-adrenergic agonist components in similar compositions without the SECs.

In one embodiment, the alpha-2-adrenergic agonist components include imino-imidazolines, imidazolines, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. Preferably, the alpha-2-adrenergic agonist components include quinoxaline components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and biologically compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is referred to as "Brimonidine tartrate."

In a preferred embodiment, the alpha-2-adrenergic agonist components, such as those listed above, are specific for the alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and/or alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonist components are unionized in the compositions. Preferably, the alpha-2-adrenergic agonist components are also unionized in the biological environment into which the compositions are administered.

In a useful embodiment, the SEC includes a polyanionic component. As used herein, the term "polyanionic component" refers to a chemical entity, for example, an ionically charged species, such as an ionically charged polymeric material, which includes more than one discrete anionic charge, that is multiple discrete anionic charges. Preferably, the polyanionic component is selected from polymeric materials having multiple anionic charges, and mixtures thereof.

Particularly useful polyanionic components are selected from anionic polymers derived from acrylic acid (meaning to include polymers from acrylic acid, acrylates and the like and mixtures thereof), anionic polymers derived from methacrylic acid (meaning to include polymers from methacrylic acid, methacrylates, and the like and mixtures thereof), anionic polymers derived from alginic acid (meaning to

include alginic acid, alginates, and the like and mixtures thereof), anionic polymers of amino acids (meaning to include polymers of amino acids, amino acid salts, and the like and mixtures thereof), and the like, and mixtures thereof. Very useful polyanionic components are those selected from anionic cellulose derivatives and mixtures thereof, especially carboxymethylcelluloses.

The polyanionic component preferably is sufficiently anionic to interact with or otherwise affect, in particular increase, the solubility of the alpha-2-adrenergic components. This interaction preferably is sufficient to render the alpha-2-adrenergic components substantially completely soluble at therapeutically effective concentrations. The amount of SEC in the composition preferably is in the range of about 0.1% (w/v) to about 30% (w/v), more preferably about 0.2% (w/v) to about 10% (w/v), and even more preferably about 0.2% (w/v) to about 0.6% (w/v).

The compositions include carrier components, for example, aqueous liquid carrier components. In one embodiment, the compositions have pH's of about 7 or greater, preferably about 7 to about 9, and are ophthalmically acceptable.

In a preferred embodiment, a composition is provided which includes an alpha-2-adrenergic agonist component in an amount effective to provide at least one therapeutic benefit to a patient to whom the composition is administered, an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component and an aqueous liquid carrier component. The alpha-2-adrenergic agonist component preferably comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. The anionic cellulose derivative preferably comprises a carboxymethylcellulose. The concentration of the anionic cellulose derivative in the composition should be about 0.2% (w/v) to about 0.6% (w/v).

In a preferred embodiment, the present compositions are ophthalmically acceptable, e.g. the compositions do not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered.

In one broad aspect of the invention, complexes are formed in the compositions. In one embodiment, the complexes include monomer units derived from at least one quinoxaline component. In a preferred embodiment, the complexes of the present invention are dimers. In a particularly preferred embodiment, the complexes are complexes, especially dimers, of Bromodidine tartrate.

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component and a preservative component in an effective amount to at least aid in preserving the compositions. Preferably, the preservative components include oxychloro components, such as compounds, ions, complexes and the like which are biologically acceptable, chemically stable and do not substantially or significantly detrimentally affect the an alpha-2-adrenergic agonist component in the compositions or the patients to whom the compositions are administered. Such compositions preferably are substantially free of cyclodextrins in the compositions or the patients to whom the compositions are administered.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art.

Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** is a graph of soluble Brimonidine tartrate verses pH at various carboxymethylcellulose concentrations.

DETAILED DESCRIPTION OF THE INVENTION

Compositions comprising alpha-2-adrenergic agonist components and SECs are provided. The alpha-2-adrenergic agonist components in the present compositions are made more soluble and may be more effectively utilized as therapeutic agents. The SECs employed in the present compositions may be effective in the solubilization of ionized alpha-2-adrenergic agonist components, unionized alpha-2-adrenergic agonist components or both. The present compositions include liquid carrier components and have the characteristics of liquid, for example, aqueous liquid, solutions.

Preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's greater than 7, as compared to identical alpha-2-adrenergic agonist components, at comparable concentrations, in similar compositions without the SECs. More preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's in the range of about 7 to about 10 and, as compared to identical alpha-2-adrenergic agonist components in similar compositions, at comparable concentrations, without the SECs.

Without wishing to be limited by any theory or mechanism of operation, it is believed that solubilized alpha-2-adrenergic agonist components are better able to cross the lipid membranes relative to unsolubilized alpha-2-adrenergic agonist components. It is further believed that the solubilized alpha-2-adrenergic agonist components are physically smaller and are therefore more able to physically permeate or diffuse through the lipid membranes.

In one embodiment, the SECs of this invention are capable of solubilizing the alpha-2-adrenergic agonist components in the biological environments into which they are introduced at therapeutically effective concentrations. Preferably, the biological environments into which the present compositions are introduced have pH's ranging from about 7 to about 9. For example, a composition comprising a SEC and an alpha-2-adrenergic agonist component may be administered to the cornea of an eye, which has a pH of about 7, wherein the alpha-2-adrenergic agonist component is substantially solubilized at the administered area. Furthermore, in one embodiment, the alpha-2-adrenergic agonist components solubilized by SECs at the administered area diffuse through biological lipid membranes more readily than alpha-2-adrenergic agonist components which are not solubilized by SECs. The solubilization of alpha-2-adrenergic agonist components preferably reduces irritation to sensitive tissues in contact or interacting with the alpha-2-adrenergic agonist components.

The presently useful alpha-2-adrenergic agonist components preferably are chosen to benefit from the presence of the SECs. In general, the alpha-2-adrenergic agonist components are provided with increased apparent solubility, preferably increased apparent water solubility, by the presence of the SECs.

Examples of alpha-2-adrenergic agonist components include molecules containing amines. Preferably, the alpha-

2-adrenergic agonist components are amine-containing molecules with pKa's of greater than about 7, more preferably about 7 to about 9.

Alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. As used herein, the term alpha-2 adrenergic agonist includes chemical entities, such as compounds, ions, complexes and the like, that produce a net sympatholytic response, resulting in increased accommodation, for example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or for example, to postsynaptic alpha-2 receptors on smooth muscle cells. A sympatholytic response is characterized by the inhibition, diminishment, or prevention of the effects of impulses conveyed by the sympathetic nervous system. The alpha-2 adrenergic agonists of the invention bind to the alpha-2 adrenergic receptors presynaptically, causing negative feedback to decrease the release of neuronal norepinephrine. Additionally, they also work on alpha-2 adrenergic receptors postsynaptically, inhibiting beta-adrenergic receptor-stimulated formation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2 adrenergic receptors on other intracellular pathways. Activity at either pre- or postsynaptic alpha-2 adrenergic receptors will result in a decreased adrenergic influence. Decreased adrenergic influence results in increased contraction resulting from cholinergic innervations. Alpha-2 adrenergic agonists also include compounds that have neuroprotective activity. For example, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is an alpha-2-adrenergic agonist which has a neuroprotective activity through an unknown mechanism.

Without limiting the invention to the specific groups and compounds listed, the following is a list of representative alpha-2 adrenergic agonists useful in this invention: iminoimidazolines, including clonidine, apraclonidine; imidazolines, including naphazoline, xymetazoline, tetrahydrozoline, and tramazoline; imidazoles, including detomidine, medetomidine, and dexmedetomidine; azepines, including B-HT 920 (6-allyl-2-amino-5,6,7,8 tetrahydro-4H-thiazolo[4,5-d]-azepine and B-HT 933; thiazines, including xylazine; oxazolines, including rilmenidine; guanidines, including guanabenz and guanfacine; catecholamines; and the like and derivatives thereof.

Particularly useful alpha-2-adrenergic agonists include quinoxaline components. In one embodiment, the quinoxaline components include quinoxaline, derivatives thereof and mixtures thereof. Preferably, the derivatives of quinoxaline include (2-imidozolin-2-ylamino) quinoxaline. More preferably, the derivatives of quinoxaline include 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline. The "halide" of the 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline may be a fluorine, a chlorine, an iodine, or preferably, a bromine, to form 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Even more preferably, the derivatives of quinoxaline to be used in accordance with this invention include a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, or Brimonidine tartrate.

Other useful quinoxaline derivatives are well known. For example, useful derivatives of a quinoxaline include the ones disclose by Burke et al U.S. Pat. No. 5,703,077. See also Danielwicz et al 3,890,319. Each of the disclosures of Burke et al and Danielwicz et al is incorporated in its entirety by reference herein.

The quinoxaline and derivatives thereof, for example Brimonidine tartrate, are amine-containing and preferably have pKa's of greater than 7, preferably about 7.5 to 9.

Analogs of the foregoing compounds that function as alpha-2 adrenergic agonists also are specifically intended to be embraced by the invention.

Preferably, the alpha-2-adrenergic agonists, for example the ones listed above, are effective toward activating alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonists, for example Brimonidine tartrate, are substantially unionized in the compositions. In another embodiment, the adrenergic compounds are substantially unionized in the environment to which they are administered, for example the cornea. Without wishing to be limited by any theory or mechanism of action, it is believed that the unionized forms of the adrenergic compounds facilitate their permeation across membrane lipid bilayers.

Any suitable SEC may be employed in accordance with the present invention. In one embodiment, the SECs include pyrrolinidone components. Examples of pyrrolinidone components are polyvinylpyrrolinidones and derivatives thereof. In a preferred embodiment, the SECs include polyanionic components. The useful polyanionic components include, but are not limited to, those materials which are effective in increasing the apparent solubility, preferably water solubility, of poorly soluble alpha-2-adrenergic agonist components and/or enhance the stability of the alpha-2-adrenergic agonist components and/or reduce unwanted side effects of the alpha-2-adrenergic agonist components. Furthermore, the polyanionic component is preferably ophthalmically acceptable at the concentrations used. Additionally, the polyanionic component preferably includes three (3) or more anionic (or negative) charges. In the event that the polyanionic component is a polymeric material, it is preferred that each of the repeating units of the polymeric material include a discrete anionic charge. Particularly useful anionic components are those which are water soluble, for example, soluble at the concentrations used in the presently useful liquid aqueous media, such as a liquid aqueous medium containing the alpha-2-adrenergic components.

The polyanionic component is preferably sufficiently anionic to interact with the alpha-2-adrenergic agonist component. Such interaction is believed to be desirable to solubilize the alpha-2-adrenergic agonist component and/or to maintain such alpha-2-adrenergic agonist component soluble in the carrier component, for example a liquid medium.

Polyanionic components also include one or more polymeric materials having multiple anionic charges.

Examples include:

- metal carboxymethylstarchs
- metal carboxymethylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - metal acrylates and methacrylates
  - alginic acid
  - metal alginates
  - vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - p-styrenesulfonic acid

metal p-styrenesulfonate
2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

In another embodiment, the polyanionic components include anionic polysaccharides which tend to exist in ionized forms at higher pH's, for example, pH's of about 7 or higher. The following are some examples of anionic polysaccharides which may be employed in accordance with this invention.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose.

Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks.

Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of which can be sulfated or nonsulfated, joined by alternating 1-3 and beta 1-4 glycosidic linkages. Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss.

Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water.

Other anionic polysaccharides found useful in the present invention are hydrophilic colloidal materials and include the natural gums such as gellan gum, alginate gums, i.e., the ammonium and alkali metal salts of alginic acid and mixtures thereof. In addition, chitosan, which is the common name for deacetylated chitin is useful. Chitin is a natural product comprising poly-(N-acetyl-D-glucosamine). Gellan gum is produced from the fermentation of pseudomonas elodea to yield an extracellular heteropolysaccharide. The alginates and chitosan are available as dry powders from Protan, Inc., Commack, N.Y. Gellan gum is available from the Kelco Division of Merk & Co., Inc., San Diego, Calif.

Generally, the alginates can be any of the water-soluble alginates including the alkali metal alginates, such as sodium, potassium, lithium, rubidium and cesium salts of alginic acid, as well as the ammonium salt, and the soluble alginates of an organic base such as mono-, di-, or triethanolamine alginates, aniline alginates, and the like. Generally, about 0.2% to about 1% by weight and, preferably, about 0.5% to about 3.0% by weight of gellan, alginate or chitosan ionic polysaccharides, based upon the total weight of the composition, are used to obtain the gel compositions of the invention.

Preferably, the anionic polysaccharides are cyclized. More preferably, the cyclized anionic polysaccharides include less than ten monomer units. Even more preferably, the cyclized polysaccharides include less than six monomer units.

In one embodiment, a particularly useful group of cyclized anionic polysaccharides includes the cyclodextrins. Examples of the cyclodextrin group include, but are not limited to: α-cyclodextrin, derivatives of α-cyclodextrin, β-cyclodextrin, derivatives of β-cyclodextrin, γ-cyclodextrin, derivatives of γ-cyclodextrin, carboxymethyl-β-cyclodextrin, carboxymethyl-ethyl-β-cyclodextrin, diethyl-β-cyclodextrin, dimethyl-β-cyclodextrin, methyl-β-cyclodextrin, random methyl-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and the like and mixtures thereof. Sulfobutylether-β-cyclodextrin is a preferred cyclized anionic polyasaccharide in accordance with the present invention. It is advantageous that the SEC's, including the above mentioned cyclodextrins, employed in this invention be, at the concentration employed, non-toxic to the mammal, human, to inhibit the present incorporation is administered. As used herein, the term "derivatives" as it relates to a cyclodextrin means any substituted or otherwise modified compound which has the characteristic chemical structure of a cyclodextrin sufficiently to function as a cyclodextrin component, for example, to enhance the solubility and/or stability of active components and/or reduce unwanted side effects of the active components and/or to form inclusive complexes with active components, as described herein.

Although cyclodextrins and/or their derivatives may be employed as SECs, one embodiment of the invention may include SECs other than cyclodextrins and/or their derivatives.

A particularly useful and preferred class of polyanionic component includes anionic cellulose derivatives. Anionic cellulose derivatives include metal carboxymethylcelluloses, metal carboxymethylhydroxyethylcelluloses and hydroxypropylmethylcelluloses and derivatives thereof.

The present polyanionic components often can exist in the unionized state, for example, in the solid state, in combination with a companion or counter ion, in particular a plurality of discrete cations equal in number to the number of discrete anionic charges so that the unionized polyanionic component is electrically neutral. For example, the present unionized polyanionic components may be present in the acid form and/or in combination with one or more metals. Since the polyanionic components are preferably ophthalmically acceptable, it is preferred that the metal associated with the unionized polyanionic component be ophthalmically acceptable in the concentrations used. Particularly useful metals include the alkali metals, for example, sodium and potassium, the alkaline earth metals, for example, calcium and magnesium, and mixtures thereof. Sodium is very useful to provide the counter ion in the unionized polyanionic component. Polyanionic components which, in the unionized states, are combined with cations other than H^+ and metal cations can be employed in the present invention.

The amount of SEC in the present compositions is not of critical importance so long as solubility at the alpha-2-adrenergic agonist component is at least somewhat increased and is present in a biologically acceptable amount. Such amount should be effective to perform the desired function or functions in the present composition and/or after administration to the human or animal. In one embodiment, the amount of SEC, preferably the polyanionic component, is sufficient to complex at least in a major amount, and more preferably substantially all, of the alpha-2-adrenergic agonist component in the present composition. In one useful embodiment, the amount of polyanionic component in the present composition is in the range of about 0.1% to about 30% (w/v) or more of the composition. Preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 10% (w/v). More preferably, the amount of polyanionic component is in the range of about 0.2%

(w/v) to about 0.6% (w/v). Even more preferably, the polyanionic component is carboxymethylcellulose and is present in the composition in the range of about 0.2% (w/v) to about 0.6% (w/v). A particularly useful concentration of carboxymethylcellulose in the present compositions is about 0.5%.

In one embodiment, the SECs, for example a carboxymethylcellulose, assist in solubilizing the alpha-2-adrenergic agonist components in the compositions. Although the SECs are capable aiding in the solubilization of ionized alpha-2-adrenergic agonist components, it is preferable that the SECs used in this invention could assist in the solubilization of unionized alpha-2-adrenergic agonist components. For example, in one embodiment, carboxymethylcellulose may help solubilize ionized alpha-2-adrenergic agonist components. In another embodiment, carboxymethylcellulose may help solubilize unionized alpha-2-adrenergic agonist components. In a preferred embodiment, the carboxylmethylcellulose helps solubilize ionized Brimonidine tartrate in the compositions. More preferably, the carboxylmethylcellulose helps solubilize unionized Brimonidine tartrate in the compositions.

In one embodiment, the compositions may also include preservative components or components which assist in the preservation of the composition. The preservative components selected so as to be effective and efficacious as preservatives in the present compositions, that is in the presence of polyanionic components, and preferably have reduced toxicity and more preferably substantially no toxicity when the compositions are administered to a human or animal.

Preservatives or components which assist in the preservation of the composition which are commonly used in pharmaceutical compositions are often less effective when used in the presence of solubilizing agents. In certain instances, this reduced preservative efficacy can be compensated for by using increased amounts of the preservative. However, where sensitive or delicate body tissue is involved, this approach may not be available since the preservative itself may cause some adverse reaction or sensitivity in the human or animal, to whom the composition is administered.

Preferably, the present preservative components or components which assist in the preservation of the composition, preferably the alpha-2-adrenergic agonist components therein, are effective in concentrations of less than about 1% (w/v) or about 0.8% (w/v) and may be 500 ppm (w/v) or less, for example, in the range of about 10 ppm(w/v) or less to about 200 ppm(w/v). Preservative components in accordance with the present invention preferably include, but are not limited to, those which form complexes with the polyanionic component to a lesser extent than does benzalkonium chloride.

Very useful examples of the present preservative components include, but are not limited to oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof. Specific examples of oxy-chloro components useful as preservatives in accordance with the present invention include hypochlorite components, for example hypochlorites; chlorate components, for example chlorates; perchlorate components, for example perchlorates; and chlorite components. Examples of chlorite components include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures therefor. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Purite T by Allergan, Inc. Other examples of oxidative preservative components includes peroxy components. For example, trace amounts of peroxy components stabilized with a hydrogen peroxide stabilizer, such as diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid, may be utilized as a preservative for use in components designed to be used in the ocular environment. Also, virtually any peroxy component may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. Examples of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, may not be stabilized utilizing the present system. See, for example, Martin et al U.S. Pat. No. 5,725,887, the disclosure of which is incorporated in its entirety herein by reference.

Preservatives other than oxidative preservative components may be included in the compositions. The choice of preservatives may depend on the route of administration. Preservatives suitable for compositions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic compositions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds and the like known generically as "benzalkonium chloride." For compositions to be administered by inhalation, however, the preferred preservative is chlorbutol and the like. Other preservatives which may be used, especially for compositions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and mixtures thereof, such as the mixture of methyl, ethyl, propyl, butyl esters and the like which is sold under the trade name "Nipastat."

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component, a preservative component in an effective amount to at least aid in preserving, preferably in an amount effective to preserve, the compositions and a liquid carrier component. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which (1) do not substantially or significantly detrimentally affect the alpha-2-adrenergic agonist components in the compositions or the patients to whom the compositions are administered, and (2) are substantially biologically acceptable and chemically stable. Such compositions in accordance with the present invention comprise an alpha-2-adrenergic agonist component, an oxy-chloro component, and a liquid carrier component, and preferably are substantially free of cyclodextrins.

The carrier components useful in the present invention are selected to be non-toxic and have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. In one embodiment, the carrier component is a liquid carrier. In a preferred embodiment, the carrier component is a liquid aqueous carrier component. A

particularly useful aqueous liquid carrier component is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution. The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5. The liquid medium preferably has an ophthalmically acceptable tonicity level, for example, of at least about 200 mOsmol/kg, more preferably in the range of about 200 to about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the carrier component substantially corresponds to the tonicity of the fluids of the eye, in particular the human eye.

In one embodiment, the carrier components containing the SECs and the alpha-2-adrenergic agonist components may have viscosities of more than about 0.01 centipoise (cps) at 25° C., preferably more than about 1 cps at 25° C., even more preferably more than about 10 cps at 25° C. In a preferred embodiment, the composition has a viscosity of about 50 cps at 25° C. and comprises a conventional buffer saline solution, a carboxymethylcellulose and a Brimonidine tartrate.

In order to insure that the pH of the aqueous liquid carrier component, and thus the pH of the composition, is maintained within the desired range, the aqueous liquid carrier component may include at least one buffer component. Although any suitable buffer component may be employed, it is preferred to select such component so as not to produce a significant amount of chlorine dioxide or evolve significant amounts of gas, such as CO_2. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components are advantageously used in the present invention.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid aqueous carrier component and do not have deleterious or toxic properties which could harm the human or animal to whom the present compositions are administered. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring agents, surface active agents, thickeners, lubricants, and the like, for example, such additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gun tragacanth and gun acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof. Such aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gun tragacanth, naturally-occurring phosphatides, for example, soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

In one broad aspect of the invention, complexes are formed in the present compositions. In one embodiment, the complexes include at least one monomer unit of a quinoxaline component. Examples of quinoxaline components include quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts thereof, esters thereof, other derivatives thereof, and the like and mixtures thereof. For example, in one embodiment, a complex of the present invention may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units. In another embodiment, the complex may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units and Brimonidine tartrate monomer units.

In a preferred embodiment, the complexes of the present invention are dimers. For example, a dimer in accordance with the present invention may include a quinoxaline and a 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Preferably, a dimer in accordance with the present invention includes two Brimonidine tartrate monomer units.

Without wishing to limit the invention to any theory or mechanism of operation, it is believed that any peroxide forming agent or strong oxidizing agent such as the oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof may facilitate the formation of the complexes, preferably complexes of alpha-2-adrenergic agonist components. For example, dimers of Brimonidine tartrate monomer units are believed to be formed in the presence of chlorites, preferably stabilized chlorine dioxide.

Furthermore, it is believed that the interactions between the monomers which serve to hold the monomers or mono-

mer subunits together to form a complex, preferably an oligomer and more preferably a dimer, may include, but not limited to, covalent bonding, ionic bonding, hydrophobic bonding, electrostatic bonding, hydrogen bonding, other chemical and/or physical interactions, and the like and combinations thereof. Such complexes may disassociate in liquid, for example, aqueous liquid, media. In one embodiment, the monomers or monomer subunits are held together by other than covalent bonding. In one embodiment, the monomers or monomer subunits are held together by electrostatic bonding or forces.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Brimonidine tartrate has a pKa of about 7.78. The pH-solubility profile of 0.5% (w/v) Brimonidine tartrate in a formulation, Ophthalmic Solution, was established in the pH range of about 5 to about 8 at 23° C. Table 1. It will be understood that concentrations of adrenergic agonists other than 0.5% may be used, so long as they have therapeutic activity. Likewise, the temperature may be varied, for example, solubility curves may be performed at 37° C. (98.6° F.). The formulation vehicle was prepared by first dissolving polyvinyl alcohol (PVA) in water. The PVA was added to approximately ⅓ of the required total amount of purified water with constant stirring. The slurry was stirred for 20–30 minutes and then heated to 80–95° C. with constant stirring. The mixture was removed from the heat source within 1 hour after having reached the temperature of 80–90° C. and stirred for an additional 10 minutes to ensure homogeneity (Part I). The other ingredients of the Ophthalmic Solution, except for Brimonidine tartrate, were dissolved in a separate container with an additional ⅓ of the required total amount of purified water (Part II). The PVA mixture (Part I) was then quantitatively transferred to Part II using several rinse volumes of purified water. The solution was adjusted to final volume with purified water without pH adjustment.

Brimonidine tartrate was weighed and transferred to a 10 mL test tube containing 5 mL of the formulation vehicle described above. The pH of each sample was then adjusted to a desired value using dilute sodium hydroxide and/or dilute hydrochloric acid. The samples were placed in a rack on a stir plate and stirred at high speed to achieve uniform mixing for 2 days; a partition was placed between the rack and the stir plate to prevent any heat diffusion from the stir plate to the samples. The temperature of the laboratory was monitored throughout the study and was found to be 23±1° C.

At the end of two days of stirring, the pH value of each sample was measured, and then approximately 1 mL of each sample was placed in a micro centrifuge tube (polypropylene) and centrifuged at 4,000 rpm for 10 minutes. The supernatant was filtered through a 1 μm filter unit (Whatman, 13 mm, PTFE). The first 3–4 drops of the filtrate were discarded; the rest of the filtrate was received and diluted quantitatively with HPLC mobile phase. The dilute sample was then injected directly on the HPLC column (Dupont Zorbax, 250 mm×4.6 mm, 5 μm) for Brimonidine tartrate assay in order to quantify the amount of Brimonidine tartrate. A control of 10.05% Brimonidine tartrate was prepared in the formulation vehicle at pH 6.3–6.5 and assayed before (untreated) and after (treated) centrifugation and filtration. This was done to evaluate the potential loss of Brimonidine tartrate in these two steps of the sample preparation. To ensure reproducibility, the study was repeated on consecutive days.

TABLE I

0.5% Brimonidine tartrate in Ophthalmic Solution.

Ingredient	Percent (w/v)
Brimonidine tartrate	0.50
Benzalkonium Chloride, NF	0.0050
Polyvinyl Alcohol, USP	1.4
Sodium Chloride, USP	0.66
Sodium Citrate, Dihydrate, USP	0.45
Hydrochloric Acid, NF or Sodium Hydroxide, NF for pH adjustment	5–8
Purified Water, USP	QS

The solubility data for Brimonidine tartrate in the formulation vehicles are presented in Table II. The results show that the solubility of Brimonidine tartrate is highly pH-dependent and spans more than two orders of magnitude over the pH range of 5–8. The solubility decreases sharply as the pH increases. The results for the treated and untreated controls are very close, suggesting that centrifugation and filtration does not cause any significant loss of Brimonidine tartrate. The two solubility profiles obtained on consecutive days agree with each other.

TABLE II

Solubility of Brimonidine tartrate in the Ophthalmic Solution Over pH Range of 5 to 8.

	STUDY 1		STUDY 2	
Sample	pH[a]	Solubility[e]	pH[a]	Solubility[e]
1	5.55	≧1644[b]	5.50	≧200.6[b]
2	5.92	132.6	5.92	160.8
3	6.14	30.4	6.06	50.1
4	6.57	7.55	6.90	3.19
5	7.00	2.69	7.40	1.19
6	7.45	1.17	7.77	0.63
7	7.83	0.62	7.86	0.58
8	—	—	7.88	0.54
Control / (untreated)	—	0.486[c]	—	—
Control / (treated)	—	0.484[d]	—	—

[a]Measured after stirring for two-days before sample withdrawal for centrifugation and filtration.
[b]Represents theoretical concentration based on sample weight. The sample solution was clear indicating that all of the Brimonidine tartrate had dissolved.
[c]Concentration of Brimonidine tartrate in control before centrifugation and filtration step.
[d]Concentration of Brimonidine tartrate in control after centrifugation and filtration step.
[e]% w/v.

EXAMPLE 2

The pH-solubility profiles of Brimonidine tartrate in compositions (solutions) containing SECs and oxy-chloro components were determined. Particularly, the effects of sodium carboxymethylcellulose (CMC), an SEC, on the solubility of Brimonidine tartrate at various pH conditions were determined. The various concentrations of CMC tested with Brimonidine tartrate were 0%, 0.056%, 0.17%, 0.5%, 1.5% (w/v), Table III.

The samples tested also contained isotonic components, buffer components, and stabilized chlorine dioxide (Purite™), Table III. Sodium carboxymethyl-cellulose, sodium chloride, potassium chloride, calcium chloride

dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

TABLE III

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	
Brimonidine tartrate	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
CMC	0.0%	0.056%	0.17%	0.5%	1.5%	(w/v)
Stabilized chlorine dioxide[a]	0.005%	0.005%	0.005%	0.005%	0.005%	(w/v)
Sodium chloride	0.58%	0.58%	0.58%	0.58%	0.58%	(w/v)
Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)
Calcium chloride, dihydrate	0.02%	0.02%	0.02%	0.02%	0.02%	(w/v)
magnesium chloride, hexahydrate	0.006%	0.006%	0.006%	0.006%	0.006%	(w/v)
boric acid	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
sodium tetraborate, decahydrate	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)

[a]Sold under the trademark Purite ™ by Allergan, Inc.

Each sample (1 through 5) was subjected to a range of pH's from about 7 to about 10. The vials containing the sample solutions were placed on a laboratory rotator and left for equilibration for fifteen days at room temperature (~21° C.). The sample solutions were filtered using a 25 mm diameter polysulfone cellulose acetate syringe type filter with 0.45 μm pore size. The filtered solutions were assayed for Brimonidine.

Conventional HPLC and detection techniques were used to detect and determine the concentrations of soluble Brimonidine tartrate. Table IV. The solubility is plotted against pH for each CMC concentration. The experimental data points were fitted to a modified Henderson-Hasselbalch equation using a nonlinear least squares routine (Deltagraph version 4.0 DeltaPoint, Inc.), FIG. **1**. The R^2 values show the goodness of fit between the experimental values and the theoretical equation to be better than 0.991.

TABLE IV

	Solubility of Brimonidine tartrate (%)				
	0% CMC	0.056% CMC	0.17% CMC	0.5% CMC	1.5% CMC
pH					
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
7.56				0.1451	
7.68	0.0786				
7.77		0.0721			
7.81			0.0735		
8.10					0.0498
8.46				0.0313	
8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

FIG. **1** clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.056% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.5%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

EXAMPLE 3

Brimonidine Tartrate Dimers.

Brimonidine tartrate is added to a test tube containing a composition including chlorite. The test tube was allowed to equilibrate for ten days. Samples obtained from the test tube is analyzed. It is observed that a portion of the Brimonidine tartrate monomer units conjugated to form dimers.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

What is claimed is:

1. A therapeutically effective aqueous ophthalmic composition comprising:

up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at about 21° C.

2. The composition of claim **1** which includes up to 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

3. The composition of claim **1** which includes about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.

4. The composition of claim **1** which includes 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

5. The composition of claim **1** having a pH of 7.0 or greater.

6. The composition of claim **1** which further comprises a preservative selected from the group consisting of an oxychloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

7. The composition of claim **6** wherein the oxy-chloro component comprises a chlorite component.

8. The composition of claim **1** which is substantially free of anionic cellulosic derivatives.

9. The composition of claim **1** which is substantially free of carboxymethyl cellulose.

10. A therapeutically effective aqueous ophthalmic composition comprising:

up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the composition at about 21° C.

11. The composition of claim **10** which includes up to 0.15% (w/v) of the component.

12. The composition of claim **10** which includes about 0.15% (w/v) of the component.

13. The composition of claim **10** which includes 0.15% (w/v) of the component.

14. The composition of claim **10** having a pH of 7.0 or greater.

15. The composition of claim **10**, which further comprises an oxy-chloro component in an amount effective to at least assist in preserving the composition.

16. The composition of claim **15** wherein the oxy-chloro component comprises a chlorite component.

17. The composition of claim **10** which is substantially free of anionic cellulosic derivatives.

18. The composition of claim **10** which is substantially free of carboxymethyl cellulose.

19. The composition of claim **6** in which the preservative comprises benzalkonium chloride.

20. The composition of claim **10** which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

21. The composition of claim **20** in which the preservative comprises benzalkonium chloride.

22. The composition of claim **20** in, which the preservative comprises a oxy-chloro component.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

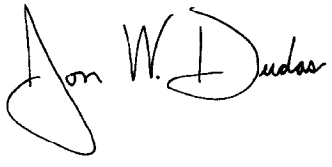
PATENT NO. : 6,641,834 B2
DATED : November 4, 2003
INVENTOR(S) : Olejnik et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10,
Line 10, delete "Purite T" and insert in place thereof -- Purite™ --

Signed and Sealed this

Twentieth Day of January, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,641,834 B2
DATED : November 4, 2003
INVENTOR(S) : Olejnik et al.

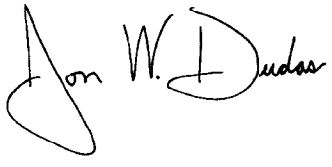
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 3,
Line 48, delete "Bromodidine" and insert in place thereof -- Brimonidine --

Column 5,
Line 61, delete "disclose" and insert in place thereof -- disclosed --

Signed and Sealed this

Twenty-fourth Day of February, 2004



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PATENT NUMBER and ISSUE 6641834

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WHICH CLAIMS BENEFIT OF 60/218,200 07/14/2000

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NONE

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Foreign priority claimed	☐ yes ☒ no		ATTORNEY DOCKET NO
35 USC 119 conditions met	☐ yes ☒ no		D-2892CON
Verified and Acknowledged Examiner's initials	RB		

TITLE : Compositions containing alpha-2-adrenergic agonist components

U.S.DEPT. OF COMM./PAT.& TM-PTO-436L(Rev. 12-94)

9-29-03 [illegible] 9-5-02

NOTICE OF ALLOWANCE MAILED		CLAIMS ALLOWED	
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ISSUE FEE		**DRAWING**	
Amount Due 1,370	Date Paid 6-11-04 CV	Sheets Drwg. 1	Figs.Drwg. 1 / Print Fig. 1
☑ TERMINAL DISCLAMER	THURMAN K. PAGE SUPERVISORY PATENT EXAMINER TECHNOLOGY CENTER 1600 Primary Examiner	J. TUCK Application Examiner	
	PREPARED FOR ISSUE		

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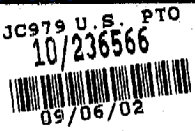

INITIALS

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SEARCH

Class	Sub.	Date	Exmr.
424	661	12/10/02	RB
424	400	↓	↓
424	427	↓	↓
↓	401	↓	↓
	422		
514	772.4	↓	↓
	772.6		
to date		5-21-03	RB
Sub 514	249	↓	↓

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
424	661	5-21-03	RB
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	427		
	401		
	422		
514	772.4		
	772.6		
	249		

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

	Date	Exmr.
inventor name search	12/10/02	RB
EAST	↓	↓
guanosine		
oxy-chlor~~o~~		
chlorite		
ophthalmically		
Medline		
STN		
Caplus		
USPATFULL		
Biosis		
Allowable subject matter per Tarnes Speece	2-21-03	RB
To Date	5-21-03	RB

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ISSUING CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)							
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)						
424	427	424	400	401	466	422			
INTERNATIONAL CLASSIFICATION		514	772.4	772.6	249				
A61K	33/14								
A61K	9/00								
A61K	9/08								
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US006641834B2

(12) **United States Patent**
Olejnik et al.

(10) **Patent No.: US 6,641,834 B2**
(45) **Date of Patent: *Nov. 4, 2003**

(54) **COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS**

(75) Inventors: **Orest Olejnik**, Coto de Coza, CA (US); **Edward D. S. Kerslake**, Charlestown, MA (US)

(73) Assignee: **Allergan Sales, Inc.**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 18 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/236,566**

(22) Filed: **Sep. 6, 2002**

(65) **Prior Publication Data**

US 2003/0027811 A1 Feb. 6, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/904,018, filed on Jul. 10, 2001.

(60) Provisional application No. 60/218,200, filed on Jul. 14, 2002.

(51) **Int. Cl.**[7] **A61K 33/14**; A61K 9/00; A61K 9/08

(52) **U.S. Cl.** **424/427**; 424/400; 424/401; 424/466; 424/422; 514/772.4; 514/772.6; 514/249

(58) **Field of Search** 424/661, 400, 424/427, 401, 422; 514/772.4, 772.6, 249

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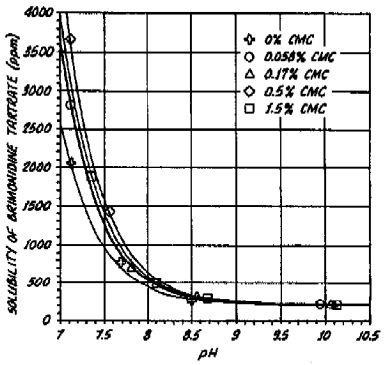
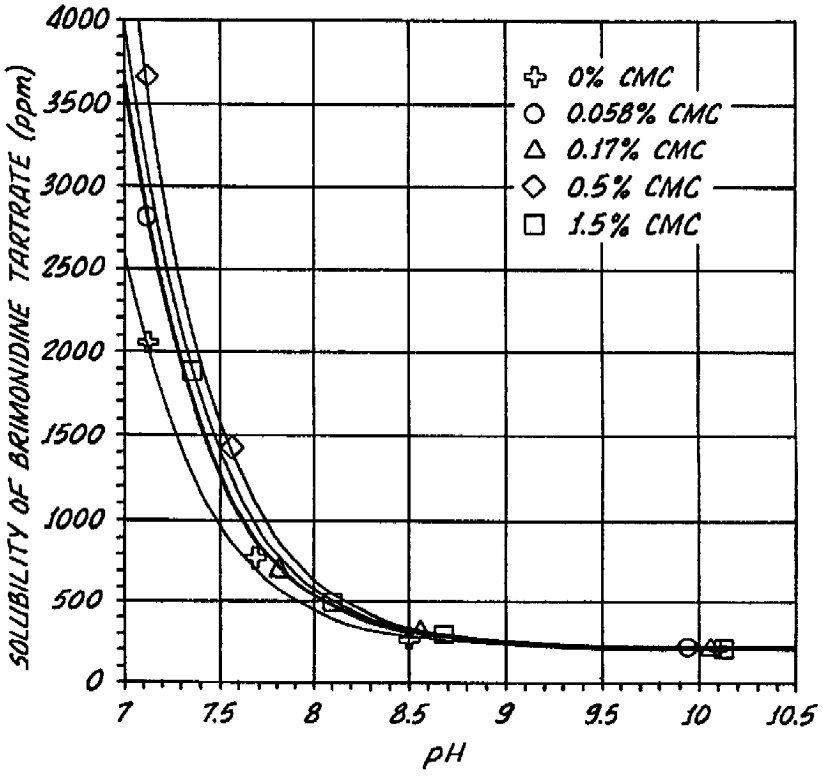
Primary Examiner—Thurman K. Page
Assistant Examiner—Rachel M. Bennett
(74) *Attorney, Agent, or Firm*—Stout, Uxa, Buyan & Mullins, LLP; Frank J. Uxa; Carlos A. Fisher

(57) **ABSTRACT**

Compositions useful for improving effectiveness of alpha-2-adrenergic agonist components include carrier components, alpha-2-adrenergic agonist components, solubility enhancing components which aid in solubilizing the alpha-2-adrenergic agonist components. In one embodiment, the alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. In another embodiment, the solubility enhancing components include carboxymethylcellulose.

22 Claims, 1 Drawing Sheet




SOLUBILITY OF BRIMONIDINE TARTRATE (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0
7
7.5
8
8.5
9
9.5
10
10.5
pH
0% CMC
0.058% CMC
0.17% CMC
0.5% CMC
1.5% CMC

COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of application Ser. No. 09/904,018, filed Jul. 10, 2001 which, in turn, claims the benefit of U.S. Provisional Application Ser. No. 60/218,200, filed Jul. 14, 2000. The disclosure of each of the above-noted applications is incorporated in its entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to compositions containing alpha-2-adrenergic agonist components. More particularly, the invention relates to such compositions in which the alpha-2-adrenergic agonist components have enhanced solubility at the therapeutically effective concentrations.

Alpha-2-adrenergic agonist components include chemical entities, such as compounds, ions, complexes and the like, which are effective to act on or bind to Alpha-2-adrenergic receptors and provide a therapeutic effect. Alpha-2-adrenergic agonist components means the agonists themselves and any and all precursors thereof, metabolites thereof and combinations thereof. One of the continuing challenges of formulating compositions having alpha-2-adrenergic agonist components is to render such components more effective. For example, alpha-2-adrenergic agonist components in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration.

Additionally, the dispensed or administered alpha-2-adrenergic agonist components should advantageously be soluble in biological systems or environments, for example, for effective or enhanced in vivo diffusion through cell membranes or lipid bilayers. Some alpha-2-adrenergic agonist components with higher pKa's, for example, greater than about 7, tend to diffuse very well through lipid membranes at pH valves near their pka, because in such circumstances they are predominantly unionized in neutral to alkaline biological environments. However, some of these alpha-2-adrenergic agonist components become insoluble at neutral to alkaline biological pH's. Such insolubility may decrease membrane diffusion capabilities, rendering the alpha-2-adrenergic agonist components less effective and/or their therapeutic effects more variable at a given dosage. Furthermore, solubilized alpha-2-adrenergic agonist components provide other benefits, for example, reduced irritation to tissues that interact with alpha-2-adrenergic agonist components.

There continues to be a need for new compositions containing alpha-2-adrenergic agonist components.

SUMMARY OF THE INVENTION

New alpha-2-adrenergic agonist component-containing compositions have been discovered. The present compositions contain certain materials which are effective in at least aiding or assisting in solubilizing the alpha-2-adrenergic agonist components in the compositions, and preferably in environments to which the compositions are administered or introduced, for example, biological environments, such as the human eye. Preferably, solubilization of the alpha-2-adrenergic agonist components in accordance with the present invention facilitates transport of such components across lipid membranes. Also, preferably such solubilization

allows the provision of more reliable and reproducible dosage forms of the drug. In addition, alpha-2-adrenergic agonist component-containing compositions have been discovered which include preservatives which provide substantial advantages, for example, reduced adverse interactions with the alpha-2-adrenergic agonist components and/or with the patients to whom the compositions are administered, while maintaining preservative effectiveness.

The present compositions preferably enhance the effectiveness of alpha-2-adrenergic agonist components by increasing the apparent water solubility of the alpha-2-adrenergic agonist components, preferably at pH's higher than neutral. The present compositions include, in addition to the adrenergic agonist components, solubility enhancing components (SECs) in amounts effective to enhance the solubility of the alpha-2-adrenergic agonist components. Preferably, the alpha-2-adrenergic agonist components are more soluble in the present compositions having, for example, pH's of about 7 or greater, relative to similar compositions without the SECs. In another embodiment, the alpha-2-adrenergic agonist components of the present compositions are more soluble in neutral, preferably alkaline, biological environments into which the compositions are administered relative to alpha-2-adrenergic agonist components in similar compositions without the SECs.

In one embodiment, the alpha-2-adrenergic agonist components include imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. Preferably, the alpha-2-adrenergic agonist components include quinoxaline components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and biologically compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is referred to as "Brimonidine tartrate."

In a preferred embodiment, the alpha-2-adrenergic agonist components, such as those listed above, are specific for the alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and/or alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonist components are unionized in the compositions. Preferably, the alpha-2-adrenergic agonist components are also unionized in the biological environment into which the compositions are administered.

In a useful embodiment, the SEC includes a polyanionic component. As used herein, the term "polyanionic component" refers to a chemical entity, for example, an ionically charged species, such as an ionically charged polymeric material, which includes more than one discrete anionic charge, that is multiple discrete anionic charges. Preferably, the polyanionic component is selected from polymeric materials having multiple anionic charges, and mixtures thereof.

Particularly useful polyanionic components are selected from anionic polymers derived from acrylic acid (meaning to include polymers from acrylic acid, acrylates and the like and mixtures thereof), anionic polymers derived from methacrylic acid (meaning to include polymers from methacrylic acid, methacrylates, and the like and mixtures thereof), anionic polymers derived from alginic acid (meaning to

include alginic acid, alginates, and the like and mixtures thereof), anionic polymers of amino acids (meaning to include polymers of amino acids, amino acid salts, and the like and mixtures thereof), and the like, and mixtures thereof. Very useful polyanionic components are those selected from anionic cellulose derivatives and mixtures thereof, especially carboxymethylcelluloses.

The polyanionic component preferably is sufficiently anionic to interact with or otherwise affect, in particular increase, the solubility of the alpha-2-adrenergic components. This interaction preferably is sufficient to render the alpha-2-adrenergic components substantially completely soluble at therapeutically effective concentrations. The amount of SEC in the composition preferably is in the range of about 0.1% (w/v) to about 30% (w/v), more preferably about 0.2% (w/v) to about 10% (w/v), and even more preferably about 0.2% (w/v) to about 0.6% (w/v).

The compositions include carrier components, for example, aqueous liquid carrier components. In one embodiment, the compositions have pH's of about 7 or greater, preferably about 7 to about 9, and are ophthalmically acceptable.

In a preferred embodiment, a composition is provided which includes an alpha-2-adrenergic agonist component in an amount effective to provide at least one therapeutic benefit to a patient to whom the composition is administered, an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component and an aqueous liquid carrier component. The alpha-2-adrenergic agonist component preferably comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. The anionic cellulose derivative preferably comprises a carboxymethylcellulose. The concentration of the anionic cellulose derivative in the composition should be about 0.2% (w/v) to about 0.6% (w/v).

In a preferred embodiment, the present compositions are ophthalmically acceptable, e.g. the compositions do not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered.

In one broad aspect of the invention, complexes are formed in the compositions. In one embodiment, the complexes include monomer units derived from at least one quinoxaline component. In a preferred embodiment, the complexes of the present invention are dimers. In a particularly preferred embodiment, the complexes are complexes, especially dimers, of Bromodidine tartrate.

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component and a preservative component in an effective amount to at least aid in preserving the compositions. Preferably, the preservative components include oxychloro components, such as compounds, ions, complexes and the like which are biologically acceptable, chemically stable and do not substantially or significantly detrimentally affect the an alpha-2-adrenergic agonist component in the compositions or the patients to whom the compositions are administered. Such compositions preferably are substantially free of cyclodextrins in the compositions or the patients to whom the compositions are administered.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art.

Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a graph of soluble Brimonidine tartrate verses pH at various carboxymethylcellulose concentrations.

DETAILED DESCRIPTION OF THE INVENTION

Compositions comprising alpha-2-adrenergic agonist components and SECs are provided. The alpha-2-adrenergic agonist components in the present compositions are made more soluble and may be more effectively utilized as therapeutic agents. The SECs employed in the present compositions may be effective in the solubilization of ionized alpha-2-adrenergic agonist components, unionized alpha-2-adrenergic agonist components or both. The present compositions include liquid carrier components and have the characteristics of liquid, for example, aqueous liquid, solutions.

Preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's greater than 7, as compared to identical alpha-2-adrenergic agonist components, at comparable concentrations, in similar compositions without the SECs. More preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's in the range of about 7 to about 10 and, as compared to identical alpha-2-adrenergic agonist components in similar compositions, at comparable concentrations, without the SECs.

Without wishing to be limited by any theory or mechanism of operation, it is believed that solubilized alpha-2-adrenergic agonist components are better able to cross the lipid membranes relative to unsolubilized alpha-2-adrenergic agonist components. It is further believed that the solubilized alpha-2-adrenergic agonist components are physically smaller and are therefore more able to physically permeate or diffuse through the lipid membranes.

In one embodiment, the SECs of this invention are capable of solubilizing the alpha-2-adrenergic agonist components in the biological environments into which they are introduced at therapeutically effective concentrations. Preferably, the biological environments into which the present compositions are introduced have pH's ranging from about 7 to about 9. For example, a composition comprising a SEC and an alpha-2-adrenergic agonist component may be administered to the cornea of an eye, which has a pH of about 7, wherein the alpha-2-adrenergic agonist component is substantially solubilized at the administered area. Furthermore, in one embodiment, the alpha-2-adrenergic agonist components solubilized by SECs at the administered area diffuse through biological lipid membranes more readily than alpha-2-adrenergic agonist components which are not solubilized by SECs. The solubilization of alpha-2-adrenergic agonist components preferably reduces irritation to sensitive tissues in contact or interacting with the alpha-2-adrenergic agonist components.

The presently useful alpha-2-adrenergic agonist components preferably are chosen to benefit from the presence of the SECs. In general, the alpha-2-adrenergic agonist components are provided with increased apparent solubility, preferably increased apparent water solubility, by the presence of the SECs.

Examples of alpha-2-adrenergic agonist components include molecules containing amines. Preferably, the alpha-

2-adrenergic agonist components are amine-containing molecules with pKa's of greater than about 7, more preferably about 7 to about 9.

Alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. As used herein, the term alpha-2 adrenergic agonist includes chemical entities, such as compounds, ions, complexes and the like, that produce a net sympatholytic response, resulting in increased accommodation, for example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or for example, to postsynaptic alpha-2 receptors on smooth muscle cells. A sympatholytic response is characterized by the inhibition, diminishment, or prevention of the effects of impulses conveyed by the sympathetic nervous system. The alpha-2 adrenergic agonists of the invention bind to the alpha-2 adrenergic receptors presynaptically, causing negative feedback to decrease the release of neuronal norepinephrine. Additionally, they also work on alpha-2 adrenergic receptors postsynaptically, inhibiting beta-adrenergic receptor-stimulated formation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2 adrenergic receptors on other intracellular pathways. Activity at either pre- or postsynaptic alpha-2 adrenergic receptors will result in a decreased adrenergic influence. Decreased adrenergic influence results in increased contraction resulting from cholinergic innervations. Alpha-2 adrenergic agonists also include compounds that have neuroprotective activity. For example, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is an alpha-2-adrenergic agonist which has a neuroprotective activity through an unknown mechanism.

Without limiting the invention to the specific groups and compounds listed, the following is a list of representative alpha-2 adrenergic agonists useful in this invention: imino-imidazolines, including clonidine, apraclonidine; imidazolines, including naphazoline, xymetazoline, tetrahydrozoline, and tramazoline; imidazoles, including detomidine, medetomidine, and dexmedetomidine; azepines, including B-HT 920 (6-allyl-2-amino-5,6,7,8 tetrahydro-4H-thiazolo[4,5-d]-azepine and B-HT 933; thiazines, including xylazine; oxazolines, including rilmenidine; guanidines, including guanabenz and guanfacine; catecholamines; and the like and derivatives thereof.

Particularly useful alpha-2-adrenergic agonists include quinoxaline components. In one embodiment, the quinoxaline components include quinoxaline, derivatives thereof and mixtures thereof. Preferably, the derivatives of quinoxaline include (2-imidozolin-2-ylamino) quinoxaline. More preferably, the derivatives of quinoxaline include 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline. The "halide" of the 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline may be a fluorine, a chlorine, an iodine, or preferably, a bromine, to form 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Even more preferably, the derivatives of quinoxaline to be used in accordance with this invention include a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, or Brimonidine tartrate.

Other useful quinoxaline derivatives are well known. For example, useful derivatives of a quinoxaline include the ones disclose by Burke et al U.S. Pat. No. 5,703,077. See also Danielwicz et al 3,890,319. Each of the disclosures of Burke et al and Danielwicz et al is incorporated in its entirety by reference herein.

The quinoxaline and derivatives thereof, for example Brimonidine tartrate, are amine-containing and preferably have pKa's of greater than 7, preferably about 7.5 to 9.

Analogs of the foregoing compounds that function as alpha-2 adrenergic agonists also are specifically intended to be embraced by the invention.

Preferably, the alpha-2-adrenergic agonists, for example the ones listed above, are effective toward activating alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonists, for example Brimonidine tartrate, are substantially unionized in the compositions. In another embodiment, the adrenergic compounds are substantially unionized in the environment to which they are administered, for example the cornea. Without wishing to be limited by any theory or mechanism of action, it is believed that the unionized forms of the adrenergic compounds facilitate their permeation across membrane lipid bilayers.

Any suitable SEC may be employed in accordance with the present invention. In one embodiment, the SECs include pyrrolinidone components. Examples of pyrrolinidone components are polyvinylpyrrolinidones and derivatives thereof. In a preferred embodiment, the SECs include polyanionic components. The useful polyanionic components include, but are not limited to, those materials which are effective in increasing the apparent solubility, preferably water solubility, of poorly soluble alpha-2-adrenergic agonist components and/or enhance the stability of the alpha-2-adrenergic agonist components and/or reduce unwanted side effects of the alpha-2-adrenergic agonist components. Furthermore, the polyanionic component is preferably ophthalmically acceptable at the concentrations used. Additionally, the polyanionic component preferably includes three (3) or more anionic (or negative) charges. In the event that the polyanionic component is a polymeric material, it is preferred that each of the repeating units of the polymeric material include a discrete anionic charge. Particularly useful anionic components are those which are water soluble, for example, soluble at the concentrations used in the presently useful liquid aqueous media, such as a liquid aqueous medium containing the alpha-2-adrenergic components.

The polyanionic component is preferably sufficiently anionic to interact with the alpha-2-adrenergic agonist component. Such interaction is believed to be desirable to solubilize the alpha-2-adrenergic agonist component and/or to maintain such alpha-2-adrenergic agonist component soluble in the carrier component, for example a liquid medium.

Polyanionic components also include one or more polymeric materials having multiple anionic charges.

Examples include:

- metal carboxymethylstarchs
- metal carboxymethylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - metal acrylates and methacrylates
  - alginic acid
  - metal alginates
  - vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - p-styrenesulfonic acid

metal p-styrenesulfonate
2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

In another embodiment, the polyanionic components include anionic polysaccharides which tend to exist in ionized forms at higher pH's, for example, pH's of about 7 or higher. The following are some examples of anionic polysaccharides which may be employed in accordance with this invention.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose.

Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks.

Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of which can be sulfated or nonsulfated, joined by alternating 1-3 and beta 1-4 glycosidic linkages. Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss.

Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water.

Other anionic polysaccharides found useful in the present invention are hydrophilic colloidal materials and include the natural gums such as gellan gum, alginate gums, i.e., the ammonium and alkali metal salts of alginic acid and mixtures thereof. In addition, chitosan, which is the common name for deacetylated chitin is useful. Chitin is a natural product comprising poly-(N-acetyl-D-glucosamine). Gellan gum is produced from the fermentation of pseudomonas elodea to yield an extracellular heteropolysaccharide. The alginates and chitosan are available as dry powders from Protan, Inc., Commack, N.Y. Gellan gum is available from the Kelco Division of Merk & Co., Inc., San Diego, Calif.

Generally, the alginates can be any of the water-soluble alginates including the alkali metal alginates, such as sodium, potassium, lithium, rubidium and cesium salts of alginic acid, as well as the ammonium salt, and the soluble alginates of an organic base such as mono-, di-, or triethanolamine alginates, aniline alginates, and the like. Generally, about 0.2% to about 1% by weight and, preferably, about 0.5% to about 3.0% by weight of gellan, alginate or chitosan ionic polysaccharides, based upon the total weight of the composition, are used to obtain the gel compositions of the invention.

Preferably, the anionic polysaccharides are cyclized. More preferably, the cyclized anionic polysaccharides include less than ten monomer units. Even more preferably, the cyclized polysaccharides include less than six monomer units.

In one embodiment, a particularly useful group of cyclized anionic polysaccharides includes the cyclodextrins. Examples of the cyclodextrin group include, but are not limited to: α-cyclodextrin, derivatives of α-cyclodextrin, β-cyclodextrin, derivatives of β-cyclodextrin, γ-cyclodextrin, derivatives of γ-cyclodextrin, carboxymethyl-β-cyclodextrin, carboxymethyl-ethyl-β-cyclodextrin, diethyl-β-cyclodextrin, dimethyl-β-cyclodextrin, methyl-β-cyclodextrin, random methyl-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and the like and mixtures thereof. Sulfobutylether-β-cyclodextrin is a preferred cyclized anionic polyasaccharide in accordance with the present invention. It is advantageous that the SEC's, including the above mentioned cyclodextrins, employed in this invention be, at the concentration employed, non-toxic to the mammal, human, to inhibit the present incorporation is administered. As used herein, the term "derivatives" as it relates to a cyclodextrin means any substituted or otherwise modified compound which has the characteristic chemical structure of a cyclodextrin sufficiently to function as a cyclodextrin component, for example, to enhance the solubility and/or stability of active components and/or reduce unwanted side effects of the active components and/or to form inclusive complexes with active components, as described herein.

Although cyclodextrins and/or their derivatives may be employed as SECs, one embodiment of the invention may include SECs other than cyclodextrins and/or their derivatives.

A particularly useful and preferred class of polyanionic component includes anionic cellulose derivatives. Anionic cellulose derivatives include metal carboxymethylcelluloses, metal carboxymethylhydroxyethylcelluloses and hydroxypropylmethylcelluloses and derivatives thereof.

The present polyanionic components often can exist in the unionized state, for example, in the solid state, in combination with a companion or counter ion, in particular a plurality of discrete cations equal in number to the number of discrete anionic charges so that the unionized polyanionic component is electrically neutral. For example, the present unionized polyanionic components may be present in the acid form and/or in combination with one or more metals. Since the polyanionic components are preferably ophthalmically acceptable, it is preferred that the metal associated with the unionized polyanionic component be ophthalmically acceptable in the concentrations used. Particularly useful metals include the alkali metals, for example, sodium and potassium, the alkaline earth metals, for example, calcium and magnesium, and mixtures thereof. Sodium is very useful to provide the counter ion in the unionized polyanionic component. Polyanionic components which, in the unionized states, are combined with cations other than H^+ and metal cations can be employed in the present invention.

The amount of SEC in the present compositions is not of critical importance so long as solubility at the alpha-2-adrenergic agonist component is at least somewhat increased and is present in a biologically acceptable amount. Such amount should be effective to perform the desired function or functions in the present composition and/or after administration to the human or animal. In one embodiment, the amount of SEC, preferably the polyanionic component, is sufficient to complex at least in a major amount, and more preferably substantially all, of the alpha-2-adrenergic agonist component in the present composition. In one useful embodiment, the amount of polyanionic component in the present composition is in the range of about 0.1% to about 30% (w/v) or more of the composition. Preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 10% (w/v). More preferably, the amount of polyanionic component is in the range of about 0.2%

(w/v) to about 0.6% (w/v). Even more preferably, the polyanionic component is carboxymethylcellulose and is present in the composition in the range of about 0.2% (w/v) to about 0.6% (w/v). A particularly useful concentration of carboxymethylcellulose in the present compositions is about 0.5%.

In one embodiment, the SECs, for example a carboxymethylcellulose, assist in solubilizing the alpha-2-adrenergic agonist components in the compositions. Although the SECs are capable aiding in the solubilization of ionized alpha-2-adrenergic agonist components, it is preferable that the SECs used in this invention could assist in the solubilization of unionized alpha-2-adrenergic agonist components. For example, in one embodiment, carboxymethylcellulose may help solubilize ionized alpha-2-adrenergic agonist components. In another embodiment, carboxymethylcellulose may help solubilize unionized alpha-2-adrenergic agonist components. In a preferred embodiment, the carboxylmethylcellulose helps solubilize ionized Brimonidine tartrate in the compositions. More preferably, the carboxylmethylcellulose helps solubilize unionized Brimonidine tartrate in the compositions.

In one embodiment, the compositions may also include preservative components or components which assist in the preservation of the composition. The preservative components selected so as to be effective and efficacious as preservatives in the present compositions, that is in the presence of polyanionic components, and preferably have reduced toxicity and more preferably substantially no toxicity when the compositions are administered to a human or animal.

Preservatives or components which assist in the preservation of the composition which are commonly used in pharmaceutical compositions are often less effective when used in the presence of solubilizing agents. In certain instances, this reduced preservative efficacy can be compensated for by using increased amounts of the preservative. However, where sensitive or delicate body tissue is involved, this approach may not be available since the preservative itself may cause some adverse reaction or sensitivity in the human or animal, to whom the composition is administered.

Preferably, the present preservative components or components which assist in the preservation of the composition, preferably the alpha-2-adrenergic agonist components therein, are effective in concentrations of less than about 1% (w/v) or about 0.8% (w/v) and may be 500 ppm (w/v) or less, for example, in the range of about 10 ppm(w/v) or less to about 200 ppm(w/v). Preservative components in accordance with the present invention preferably include, but are not limited to, those which form complexes with the polyanionic component to a lesser extent than does benzalkonium chloride.

Very useful examples of the present preservative components include, but are not limited to oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof. Specific examples of oxy-chloro components useful as preservatives in accordance with the present invention include hypochlorite components, for example hypochlorites; chlorate components, for example chlorates; perchlorate components, for example perchlorates; and chlorite components. Examples of chlorite components include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures therefor. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Purite T by Allergan, Inc. Other examples of oxidative preservative components includes peroxy components. For example, trace amounts of peroxy components stabilized with a hydrogen peroxide stabilizer, such as diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid, may be utilized as a preservative for use in components designed to be used in the ocular environment. Also, virtually any peroxy component may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. Examples of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, may not be stabilized utilizing the present system. See, for example, Martin et al U.S. Pat. No. 5,725,887, the disclosure of which is incorporated in its entirety herein by reference.

Preservatives other than oxidative preservative components may be included in the compositions. The choice of preservatives may depend on the route of administration. Preservatives suitable for compositions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic compositions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds and the like known generically as "benzalkonium chloride." For compositions to be administered by inhalation, however, the preferred preservative is chlorbutol and the like. Other preservatives which may be used, especially for compositions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and mixtures thereof, such as the mixture of methyl, ethyl, propyl, butyl esters and the like which is sold under the trade name "Nipastat."

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component, a preservative component in an effective amount to at least aid in preserving, preferably in an amount effective to preserve, the compositions and a liquid carrier component. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which (1) do not substantially or significantly detrimentally affect the alpha-2-adrenergic agonist components in the compositions or the patients to whom the compositions are administered, and (2) are substantially biologically acceptable and chemically stable. Such compositions in accordance with the present invention comprise an alpha-2-adrenergic agonist component, an oxy-chloro component, and a liquid carrier component, and preferably are substantially free of cyclodextrins.

The carrier components useful in the present invention are selected to be non-toxic and have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. In one embodiment, the carrier component is a liquid carrier. In a preferred embodiment, the carrier component is a liquid aqueous carrier component. A

particularly useful aqueous liquid carrier component is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution. The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5. The liquid medium preferably has an ophthalmically acceptable tonicity level, for example, of at least about 200 mOsmol/kg, more preferably in the range of about 200 to about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the carrier component substantially corresponds to the tonicity of the fluids of the eye, in particular the human eye.

In one embodiment, the carrier components containing the SECs and the alpha-2-adrenergic agonist components may have viscosities of more than about 0.01 centipoise (cps) at 25° C., preferably more than about 1 cps at 25° C., even more preferably more than about 10 cps at 25° C. In a preferred embodiment, the composition has a viscosity of about 50 cps at 25° C. and comprises a conventional buffer saline solution, a carboxymethylcellulose and a Brimonidine tartrate.

In order to insure that the pH of the aqueous liquid carrier component, and thus the pH of the composition, is maintained within the desired range, the aqueous liquid carrier component may include at least one buffer component. Although any suitable buffer component may be employed, it is preferred to select such component so as not to produce a significant amount of chlorine dioxide or evolve significant amounts of gas, such as CO_2. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components are advantageously used in the present invention.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid aqueous carrier component and do not have deleterious or toxic properties which could harm the human or animal to whom the present compositions are administered. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring agents, surface active agents, thickeners, lubricants, and the like, for example, such additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gun tragacanth and gun acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof. Such aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gun tragacanth, naturally-occurring phosphatides, for example, soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

In one broad aspect of the invention, complexes are formed in the present compositions. In one embodiment, the complexes include at least one monomer unit of a quinoxaline component. Examples of quinoxaline components include quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts thereof, esters thereof, other derivatives thereof, and the like and mixtures thereof. For example, in one embodiment, a complex of the present invention may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units. In another embodiment, the complex may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units and Brimonidine tartrate monomer units.

In a preferred embodiment, the complexes of the present invention are dimers. For example, a dimer in accordance with the present invention may include a quinoxaline and a 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Preferably, a dimer in accordance with the present invention includes two Brimonidine tartrate monomer units.

Without wishing to limit the invention to any theory or mechanism of operation, it is believed that any peroxide forming agent or strong oxidizing agent such as the oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof may facilitate the formation of the complexes, preferably complexes of alpha-2-adrenergic agonist components. For example, dimers of Brimonidine tartrate monomer units are believed to be formed in the presence of chlorites, preferably stabilized chlorine dioxide.

Furthermore, it is believed that the interactions between the monomers which serve to hold the monomers or mono-

mer subunits together to form a complex, preferably an oligomer and more preferably a dimer, may include, but not limited to, covalent bonding, ionic bonding, hydrophobic bonding, electrostatic bonding, hydrogen bonding, other chemical and/or physical interactions, and the like and combinations thereof. Such complexes may disassociate in liquid, for example, aqueous liquid, media. In one embodiment, the monomers or monomer subunits are held together by other than covalent bonding. In one embodiment, the monomers or monomer subunits are held together by electrostatic bonding or forces.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Brimonidine tartrate has a pKa of about 7.78. The pH-solubility profile of 0.5% (w/v) Brimonidine tartrate in a formulation, Ophthalmic Solution, was established in the pH range of about 5 to about 8 at 23° C. Table 1. It will be understood that concentrations of adrenergic agonists other than 0.5% may be used, so long as they have therapeutic activity. Likewise, the temperature may be varied, for example, solubility curves may be performed at 37° C. (98.6° F.). The formulation vehicle was prepared by first dissolving polyvinyl alcohol (PVA) in water. The PVA was added to approximately ⅓ of the required total amount of purified water with constant stirring. The slurry was stirred for 20–30 minutes and then heated to 80–95° C. with constant stirring. The mixture was removed from the heat source within 1 hour after having reached the temperature of 80–90° C. and stirred for an additional 10 minutes to ensure homogeneity (Part I). The other ingredients of the Ophthalmic Solution, except for Brimonidine tartrate, were dissolved in a separate container with an additional ⅓ of the required total amount of purified water (Part II). The PVA mixture (Part I) was then quantitatively transferred to Part II using several rinse volumes of purified water. The solution was adjusted to final volume with purified water without pH adjustment.

Brimonidine tartrate was weighed and transferred to a 10 mL test tube containing 5 mL of the formulation vehicle described above. The pH of each sample was then adjusted to a desired value using dilute sodium hydroxide and/or dilute hydrochloric acid. The samples were placed in a rack on a stir plate and stirred at high speed to achieve uniform mixing for 2 days; a partition was placed between the rack and the stir plate to prevent any heat diffusion from the stir plate to the samples. The temperature of the laboratory was monitored throughout the study and was found to be 23±1° C.

At the end of two days of stirring, the pH value of each sample was measured, and then approximately 1 mL of each sample was placed in a micro centrifuge tube (polypropylene) and centrifuged at 4,000 rpm for 10 minutes. The supernatant was filtered through a 1 μm filter unit (Whatman, 13 mm, PTFE). The first 3–4 drops of the filtrate were discarded; the rest of the filtrate was received and diluted quantitatively with HPLC mobile phase. The dilute sample was then injected directly on the HPLC column (Dupont Zorbax, 250 mm×4.6 mm, 5 μm) for Brimonidine tartrate assay in order to quantify the amount of Brimonidine tartrate. A control of 10.05% Brimonidine tartrate was prepared in the formulation vehicle at pH 6.3–6.5 and assayed before (untreated) and after (treated) centrifugation and filtration. This was done to evaluate the potential loss of Brimonidine tartrate in these two steps of the sample preparation. To ensure reproducibility, the study was repeated on consecutive days.

TABLE I

0.5% Brimonidine tartrate in Ophthalmic Solution.

Ingredient	Percent (w/v)
Brimonidine tartrate	0.50
Benzalkonium Chloride, NF	0.0050
Polyvinyl Alcohol, USP	1.4
Sodium Chloride, USP	0.66
Sodium Citrate, Dihydrate, USP	0.45
Hydrochloric Acid, NF or Sodium Hydroxide, NF for pH adjustment	5–8
Purified Water, USP	QS

The solubility data for Brimonidine tartrate in the formulation vehicles are presented in Table II. The results show that the solubility of Brimonidine tartrate is highly pH-dependent and spans more than two orders of magnitude over the pH range of 5–8. The solubility decreases sharply as the pH increases. The results for the treated and untreated controls are very close, suggesting that centrifugation and filtration does not cause any significant loss of Brimonidine tartrate. The two solubility profiles obtained on consecutive days agree with each other.

TABLE II

Solubility of Brimonidine tartrate in the Ophthalmic Solution Over pH Range of 5 to 8.

	STUDY 1		STUDY 2	
Sample	pH[a]	Solubility[c]	pH[a]	Solubility[c]
1	5.55	≧1644[b]	5.50	≧200.6[b]
2	5.92	132.6	5.92	160.8
3	6.14	30.4	6.06	50.1
4	6.57	7.55	6.90	3.19
5	7.00	2.69	7.40	1.19
6	7.45	1.17	7.77	0.63
7	7.83	0.62	7.86	0.58
8	—	—	7.88	0.54
Control / (untreated)	—	0.486[c]	—	—
Control / (treated)	—	0.484[d]	—	—

[a]Measured after stirring for two-days before sample withdrawal for centrifugation and filtration.
[b]Represents theoretical concentration based on sample weight. The sample solution was clear indicating that all of the Brimonidine tartrate had dissolved.
[c]Concentration of Brimonidine tartrate in control before centrifugation and filtration step.
[d]Concentration of Brimonidine tartrate in control after centrifugation and filtration step.
[e]% w/v.

EXAMPLE 2

The pH-solubility profiles of Brimonidine tartrate in compositions (solutions) containing SECs and oxy-chloro components were determined. Particularly, the effects of sodium carboxymethylcellulose (CMC), an SEC, on the solubility of Brimonidine tartrate at various pH conditions were determined. The various concentrations of CMC tested with Brimonidine tartrate were 0%, 0.056%, 0.17%, 0.5%, 1.5% (w/v), Table III.

The samples tested also contained isotonic components, buffer components, and stabilized chlorine dioxide (Purite™), Table III. Sodium carboxymethyl-cellulose, sodium chloride, potassium chloride, calcium chloride

dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

TABLE III

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	
Brimonidine tartrate	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
CMC	0.0%	0.056%	0.17%	0.5%	1.5%	(w/v)
Stabilized chlorine dioxide[a]	0.005%	0.005%	0.005%	0.005%	0.005%	(w/v)
Sodium chloride	0.58%	0.58%	0.58%	0.58%	0.58%	(w/v)
Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)
Calcium chloride, dihydrate	0.02%	0.02%	0.02%	0.02%	0.02%	(w/v)
magnesium chloride, hexahydrate	0.006%	0.006%	0.006%	0.006%	0.006%	(w/v)
boric acid	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
sodium tetraborate, decahydrate	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)

[a]Sold under the trademark Purite ™ by Allergan, Inc.

Each sample (1 through 5) was subjected to a range of pH's from about 7 to about 10. The vials containing the sample solutions were placed on a laboratory rotator and left for equilibration for fifteen days at room temperature (~21° C.). The sample solutions were filtered using a 25 mm diameter polysulfone cellulose acetate syringe type filter with 0.45 μm pore size. The filtered solutions were assayed for Brimonidine.

Conventional HPLC and detection techniques were used to detect and determine the concentrations of soluble Brimonidine tartrate. Table IV. The solubility is plotted against pH for each CMC concentration. The experimental data points were fitted to a modified Henderson-Hasselbalch equation using a nonlinear least squares routine (Deltagraph version 4.0 DeltaPoint, Inc.), FIG. 1. The R^2 values show the goodness of fit between the experimental values and the theoretical equation to be better than 0.991.

TABLE IV

	Solubility of Brimonidine tartrate (%)				
	0% CMC	0.056% CMC	0.17% CMC	0.5% CMC	1.5% CMC
pH					
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
7.56				0.1451	
7.68	0.0786				
7.77		0.0721			
7.81			0.0735		
8.10					0.0498
8.46				0.0313	
8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

FIG. 1 clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.056% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.5%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

EXAMPLE 3

Brimonidine Tartrate Dimers.

Brimonidine tartrate is added to a test tube containing a composition including chlorite. The test tube was allowed to equilibrate for ten days. Samples obtained from the test tube is analyzed. It is observed that a portion of the Brimonidine tartrate monomer units conjugated to form dimers.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

What is claimed is:

1. A therapeutically effective aqueous ophthalmic composition comprising:

up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at about 21° C.

2. The composition of claim 1 which includes up to 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

3. The composition of claim 1 which includes about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.

4. The composition of claim 1 which includes 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

5. The composition of claim 1 having a pH of 7.0 or greater.

6. The composition of claim 1 which further comprises a preservative selected from the group consisting of an oxychloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

7. The composition of claim 6 wherein the oxy-chloro component comprises a chlorite component.

8. The composition of claim 1 which is substantially free of anionic cellulosic derivatives.

9. The composition of claim 1 which is substantially free of carboxymethyl cellulose.

10. A therapeutically effective aqueous ophthalmic composition comprising:

up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the composition at about 21° C.

11. The composition of claim 10 which includes up to 0.15% (w/v) of the component.

12. The composition of claim 10 which includes about 0.15% (w/v) of the component.

13. The composition of claim 10 which includes 0.15% (w/v) of the component.

14. The composition of claim 10 having a pH of 7.0 or greater.

15. The composition of claim 10, which further comprises an oxy-chloro component in an amount effective to at least assist in preserving the composition.

16. The composition of claim 15 wherein the oxy-chloro component comprises a chlorite component.

17. The composition of claim 10 which is substantially free of anionic cellulosic derivatives.

18. The composition of claim 10 which is substantially free of carboxymethyl cellulose.

19. The composition of claim 6 in which the preservative comprises benzalkonium chloride.

20. The composition of claim 10 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

21. The composition of claim 20 in which the preservative comprises benzalkonium chloride.

22. The composition of claim 20 in, which the preservative comprises a oxy-chloro component.

* * * * *

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APPLICANTS

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** CONTINUING DATA **********

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** FOREIGN APPLICATIONS **********

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☐ yes ☐ no	CA	1	20	2
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TITLE

COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

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** FOREIGN APPLICATIONS **********

NONE

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TITLE
Compositions containing alpha-2-adrenergic agonist components

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COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

ABSTRACT OF THE DISCLOSURE

Compositions useful for improving effectiveness of alpha-2-adrenergic agonist components include carrier components, alpha-2-adrenergic agonist components, solubility enhancing components which aid in solubilizing the alpha-2-adrenergic agonist components. In one embodiment, the alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. In another embodiment, the solubility enhancing components include carboxymethylcellulose.

D-2892

COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application 60/218,200 filed July 14, 2000.

BACKGROUND OF THE INVENTION

The present invention relates to compositions containing alpha-2-adrenergic agonist components. More particularly, the invention relates to such compositions in which the alpha-2-adrenergic agonist components have enhanced solubility at the therapeutically effective concentrations.

Alpha-2-adrenergic agonist components include chemical entities, such as compounds, ions, complexes and the like, which are effective to act on or bind to Alpha-2-adrenergic receptors and provide a therapeutic effect. Alpha-2-adrenergic agonist components means the agonists themselves and any and all precursors thereof, metabolites thereof and combinations thereof. One of the continuing challenges of formulating compositions having alpha-2-adrenergic agonist components is to render such components more effective. For example, alpha-2-adrenergic agonist components in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration.

Additionally, the dispensed or administered alpha-2-adrenergic agonist components should advantageously be soluble in biological systems or environments, for example, for effective or enhanced in vivo diffusion through cell membranes or lipid bilayers. Some alpha-2-adrenergic agonist components with higher pKa's, for

example, greater than about 7, tend to diffuse very well through lipid membranes at pH valves near their pka, because in such circumstances they are predominantly unionized in neutral to alkaline biological environments. However, some of these alpha-2-adrenergic agonist components become insoluble at neutral to alkaline biological pH's. Such insolubility may decrease membrane diffusion capabilities, rendering the alpha-2-adrenergic agonist components less effective and/or their therapeutic effects more variable at a given dosage. Furthermore, solubilized alpha-2-adrenergic agonist components provide other benefits, for example, reduced irritation to tissues that interact with alpha-2-adrenergic agonist components.

There continues to be a need for new compositions containing alpha-2-adrenergic agonist components.

SUMMARY OF THE INVENTION

New alpha-2-adrenergic agonist component-containing compositions have been discovered. The present compositions contain certain materials which are effective in at least aiding or assisting in solubilizing the alpha-2-adrenergic agonist components in the compositions, and preferably in environments to which the compositions are administered or introduced, for example, biological environments, such as the human eye. Preferably, solubilization of the alpha-2-adrenergic agonist components in accordance with the present invention facilitates transport of such components across lipid membranes. Also, preferably such solubilization allows the provision of more reliable and reproducible dosage forms of the drug. In addition, alpha-2-adrenergic agonist component-containing compositions have been discovered which include preservatives which provide substantial advantages, for example, reduced adverse

interactions with the alpha-2-adrenergic agonist components and/or with the patients to whom the compositions are administered, while maintaining preservative effectiveness.

The present compositions preferably enhance the effectiveness of alpha-2-adrenergic agonist components by increasing the apparent water solubility of the alpha-2-adrenergic agonist components, preferably at pH's higher than neutral. The present compositions include, in addition to the adrenergic agonist components, solubility enhancing components (SECs) in amounts effective to enhance the solubility of the alpha-2-adrenergic agonist components. Preferably, the alpha-2-adrenergic agonist components are more soluble in the present compositions having, for example, pH's of about 7 or greater, relative to similar compositions without the SECs. In another embodiment, the alpha-2-adrenergic agonist components of the present compositions are more soluble in neutral, preferably alkaline, biological environments into which the compositions are administered relative to alpha-2-adrenergic agonist components in similar compositions without the SECs.

In one embodiment, the alpha-2-adrenergic agonist components include imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. Preferably, the alpha-2-adrenergic agonist components include quinoxaline components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and biologically

compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is referred to as "Brimonidine tartrate."

In a preferred embodiment, the alpha-2-adrenergic agonist components, such as those listed above, are specific for the alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and/or alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonist components are unionized in the compositions. Preferably, the alpha-2-adrenergic agonist components are also unionized in the biological environment into which the compositions are administered.

In a useful embodiment, the SEC includes a polyanionic component. As used herein, the term "polyanionic component" refers to a chemical entity, for example, an ionically charged species, such as an ionically charged polymeric material, which includes more than one discrete anionic charge, that is multiple discrete anionic charges. Preferably, the polyanionic component is selected from polymeric materials having multiple anionic charges, and mixtures thereof.

Particularly useful polyanionic components are selected from anionic polymers derived from acrylic acid (meaning to include polymers from acrylic acid, acrylates and the like and mixtures thereof), anionic polymers derived from methacrylic acid (meaning to include polymers from methacrylic acid, methacrylates, and the like and mixtures thereof), anionic polymers derived from alginic acid (meaning to include alginic acid, alginates, and the like and mixtures thereof), anionic polymers of amino acids (meaning to include polymers of amino acids, amino

acid salts, and the like and mixtures thereof), and the like, and mixtures thereof. Very useful polyanionic components are those selected from anionic cellulose derivatives and mixtures thereof, especially carboxymethylcelluloses.

The polyanionic component preferably is sufficiently anionic to interact with or otherwise affect, in particular increase, the solubility of the alpha-2-adrenergic components. This interaction preferably is sufficient to render the alpha-2-adrenergic components substantially completely soluble at therapeutically effective concentrations. The amount of SEC in the composition preferably is in the range of about 0.1% (w/v) to about 30% (w/v), more preferably about 0.2% (w/v) to about 10% (w/v), and even more preferably about 0.2% (w/v) to about 0.6% (w/v).

The compositions include carrier components, for example, aqueous liquid carrier components. In one embodiment, the compositions have pH's of about 7 or greater, preferably about 7 to about 9, and are ophthalmically acceptable.

In a preferred embodiment, a composition is provided which includes an alpha-2-adrenergic agonist component in an amount effective to provide at least one therapeutic benefit to a patient to whom the composition is administered, an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component and an aqueous liquid carrier component. The alpha-2-adrenergic agonist component preferably comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. The anionic cellulose derivative preferably comprises a carboxymethylcellulose. The concentration of the anionic cellulose derivative in

the composition should be about 0.2% (w/v) to about 0.6% (w/v).

In a preferred embodiment, the present compositions are ophthalmically acceptable, e.g. the compositions do not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered.

In one broad aspect of the invention, complexes are formed in the compositions. In one embodiment, the complexes include monomer units derived from at least one quinoxaline component. In a preferred embodiment, the complexes of the present invention are dimers. In a particularly preferred embodiment, the complexes are complexes, especially dimers, of Bromodidine tartrate.

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component and a preservative component in an effective amount to at least aid in preserving the compositions. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which are biologically acceptable, chemically stable and do not substantially or significantly detrimentally affect the an alpha-2-adrenergic agonist component in the compositions or the patients to whom the compositions are administered. Such compositions preferably are substantially free of cyclodextrins in the compositions or the patients to whom the compositions are administered.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art.

Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a graph of soluble Brimonidine tartrate verses pH at various carboxymethylcellulose concentrations.

DETAILED DESCRIPTION OF THE INVENTION

Compositions comprising alpha-2-adrenergic agonist components and SECs are provided. The alpha-2-adrenergic agonist components in the present compositions are made more soluble and may be more effectively utilized as therapeutic agents. The SECs employed in the present compositions may be effective in the solubilization of ionized alpha-2-adrenergic agonist components, unionized alpha-2-adrenergic agonist components or both. The present compositions include liquid carrier components and have the characteristics of liquid, for example, aqueous liquid, solutions.

Preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's greater than 7, as compared to identical alpha-2-adrenergic agonist components, at comparable concentrations, in similar compositions without the SECs. More preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's in the range of about 7 to about 10 and, as compared to identical alpha-2-adrenergic agonist components in similar compositions, at comparable concentrations, without the SECs.

Without wishing to be limited by any theory or mechanism of operation, it is believed that solubilized

alpha-2-adrenergic agonist components are better able to cross the lipid membranes relative to unsolubilized alpha-2-adrenergic agonist components. It is further believed that the solubilized alpha-2-adrenergic agonist components are physically smaller and are therefore more able to physically permeate or diffuse through the lipid membranes.

In one embodiment, the SECs of this invention are capable of solubilizing the alpha-2-adrenergic agonist components in the biological environments into which they are introduced at therapeutically effective concentrations. Preferably, the biological environments into which the present compositions are introduced have pH's ranging from about 7 to about 9. For example, a composition comprising a SEC and an alpha-2-adrenergic agonist component may be administered to the cornea of an eye, which has a pH of about 7, wherein the alpha-2-adrenergic agonist component is substantially solubilized at the administered area. Furthermore, in one embodiment, the alpha-2-adrenergic agonist components solubilized by SECs at the administered area diffuse through biological lipid membranes more readily than alpha-2-adrenergic agonist components which are not solubilized by SECs. The solubilization of alpha-2-adrenergic agonist components preferably reduces irritation to sensitive tissues in contact or interacting with the alpha-2-adrenergic agonist components.

The presently useful alpha-2-adrenergic agonist components preferably are chosen to benefit from the presence of the SECs. In general, the alpha-2-adrenergic agonist components are provided with increased apparent solubility, preferably increased apparent water solubility, by the presence of the SECs.

Examples of alpha-2-adrenergic agonist components include molecules containing amines. Preferably, the alpha-2-adrenergic agonist components are amine-containing molecules with pKa's of greater than about 7, more preferably about 7 to about 9.

Alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. As used herein, the term alpha-2 adrenergic agonist includes chemical entities, such as compounds, ions, complexes and the like, that produce a net sympatholytic response, resulting in increased accommodation, for example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or for example, to postsynaptic alpha-2 receptors on smooth muscle cells. A sympatholytic response is characterized by the inhibition, diminishment, or prevention of the effects of impulses conveyed by the sympathetic nervous system. The alpha-2 adrenergic agonists of the invention bind to the alpha-2 adrenergic receptors presynaptically, causing negative feedback to decrease the release of neuronal norepinephrine. Additionally, they also work on alpha-2 adrenergic receptors postsynaptically, inhibiting beta-adrenergic receptor-stimulated formation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2 adrenergic receptors on other intracellular pathways. Activity at either pre- or postsynaptic alpha-2 adrenergic receptors will result in a decreased adrenergic influence. Decreased adrenergic influence results in increased contraction resulting from cholinergic innervations. Alpha-2 adrenergic agonists also include compounds that have neuroprotective activity. For example, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is an alpha-2-adrenergic agonist which has a neuroprotective activity through an

unknown mechanism.

Without limiting the invention to the specific groups and compounds listed, the following is a list of representative alpha-2 adrenergic agonists useful in this invention: imino-imidazolines, including clonidine, apraclonidine; imidazolines, including naphazoline, xymetazoline, tetrahydrozoline, and tramazoline; imidazoles, including detomidine, medetomidine, and dexmedetomidine; azepines, including B-HT 920 (6-allyl-2-amino-5,6,7,8 tetrahydro-4H-thiazolo[4,5-d]-azepine and B-HT 933; thiazines, including xylazine; oxazolines, including rilmenidine; guanidines, including guanabenz and guanfacine; catecholamines; and the like and derivatives thereof.

Particularly useful alpha-2-adrenergic agonists include quinoxaline components. In one embodiment, the quinoxaline components include quinoxaline, derivatives thereof and mixtures thereof. Preferably, the derivatives of quinoxaline include (2-imidozolin-2-ylamino) quinoxaline. More preferably, the derivatives of quinoxaline include 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline. The "halide" of the 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline may be a fluorine, a chlorine, an iodine, or preferably, a bromine, to form 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Even more preferably, the derivatives of quinoxaline to be used in accordance with this invention include a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, or Brimonidine tartrate.

Other useful quinoxaline derivatives are well known. For example, useful derivatives of a quinoxaline include the ones disclose by Burke et al U.S. Patent No. 5,703,077. See also Danielwicz et al 3,890,319. Each of

the disclosures of Burke et al and Danielwicz et al is incorporated in its entirety by reference herein.

The quinoxaline and derivatives thereof, for example Brimonidine tartrate, are amine-containing and preferably have pKa's of greater than 7, preferably about 7.5 to 9.

Analogs of the foregoing compounds that function as alpha-2 adrenergic agonists also are specifically intended to be embraced by the invention.

Preferably, the alpha-2-adrenergic agonists, for example the ones listed above, are effective toward activating alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonists, for example Brimonidine tartrate, are substantially unionized in the compositions. In another embodiment, the adrenergic compounds are substantially unionized in the environment to which they are administered, for example the cornea. Without wishing to be limited by any theory or mechanism of action, it is believed that the unionized forms of the adrenergic compounds facilitate their permeation across membrane lipid bilayers.

Any suitable SEC may be employed in accordance with the present invention. In one embodiment, the SECs include pyrrolinidone components. Examples of pyrrolinidone components are polyvinylpyrrolinidones and derivatives thereof. In a preferred embodiment, the SECs include polyanionic components. The useful polyanionic components include, but are not limited to, those materials which are effective in increasing the apparent solubility, preferably water solubility, of poorly soluble alpha-2-adrenergic agonist components and/or enhance the stability of the alpha-2-adrenergic agonist components and/or reduce unwanted side effects of the alpha-2-adrenergic agonist components. Furthermore, the

polyanionic component is preferably ophthalmically acceptable at the concentrations used. Additionally, the polyanionic component preferably includes three (3) or more anionic (or negative) charges. In the event that the polyanionic component is a polymeric material, it is preferred that each of the repeating units of the polymeric material include a discrete anionic charge. Particularly useful anionic components are those which are water soluble, for example, soluble at the concentrations used in the presently useful liquid aqueous media, such as a liquid aqueous medium containing the alpha-2-adrenergic components.

The polyanionic component is preferably sufficiently anionic to interact with the alpha-2-adrenergic agonist component. Such interaction is believed to be desirable to solubilize the alpha-2-adrenergic agonist component and/or to maintain such alpha-2-adrenergic agonist component soluble in the carrier component, for example a liquid medium.

Polyanionic components also include one or more polymeric materials having multiple anionic charges. Examples include:

metal carboxymethylstarchs
metal carboxymethylhydroxyethylstarchs
hydrolyzed polyacrylamides and polyacrylonitriles
heparin
homopolymers and copolymers of one or more of:
- acrylic and methacrylic acids
- metal acrylates and methacrylates
- alginic acid
- metal alginates
- vinylsulfonic acid
- metal vinylsulfonate

amino acids, such as aspartic acid, glutamic acid and the like
metal salts of amino acids
p-styrenesulfonic acid
metal p-styrenesulfonate
2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

In another embodiment, the polyanionic components include anionic polysaccharides which tend to exist in ionized forms at higher pH's, for example, pH's of about 7 or higher. The following are some examples of anionic polysaccharides which may be employed in accordance with this invention.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose.

Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks.

Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of which can be sulfated or nonsulfated, joined by alternating 1-3 and beta 1-4 glycosidic linkages.

Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss.

Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water.

Other anionic polysaccharides found useful in the present invention are hydrophilic colloidal materials and include the natural gums such as gellan gum, alginate gums, i.e., the ammonium and alkali metal salts of alginic acid and mixtures thereof. In addition, chitosan, which is the common name for deacetylated chitin is useful. Chitin is a natural product comprising poly-(N-acetyl-D-glucosamine). Gellan gum is produced from the fermentation of pseudomonas elodea to yield an extracellular heteropolysaccharide. The alginates and chitosan are available as dry powders from Protan, Inc., Commack, N.Y. Gellan gum is available from the Kelco Division of Merk & Co., Inc., San Diego, Calif.

Generally, the alginates can be any of the water-soluble alginates including the alkali metal alginates, such as sodium, potassium, lithium, rubidium and cesium salts of alginic acid, as well as the ammonium salt, and the soluble alginates of an organic base such as mono-, di-, or tri-ethanolamine alginates, aniline alginates, and the like. Generally, about 0.2% to about 1% by weight and, preferably, about 0.5% to about 3.0% by weight of gellan, alginate or chitosan ionic polysaccharides, based upon the total weight of the composition, are used to obtain the gel compositions of the invention.

Preferably, the anionic polysaccharides are cyclized. More preferably, the cyclized anionic polysaccharides include less than ten monomer units. Even more preferably, the cyclized polysaccharides include less than six monomer units.

In one embodiment, a particularly useful group of cyclized anionic polysaccharides includes the cyclodextrins. Examples of the cyclodextrin group include, but are not limited to: α-cyclodextrin, derivatives of α-cyclodextrin, β-cyclodextrin, derivatives of β-cyclodextrin, γ-cyclodextrin, derivatives of γ-cyclodextrin, carboxymethyl-β-cyclodextrin, carboxymethyl-ethyl-β-cyclodextrin, diethyl-β-cyclodextrin, dimethyl-β-cyclodextrin, methyl-β-cyclodextrin, random methyl-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and the like and mixtures thereof. Sulfobutylether-β-cyclodextrin is a preferred cyclized anionic polyasaccharide in accordance with the present invention. It is advantageous that the SEC's, including the above mentioned cyclodextrins, employed in this invention be, at the concentration employed, non-toxic to the mammal, human, to inhibit the present incorporation is administered . As used herein, the term "derivatives" as it relates to a cyclodextrin means any substituted or otherwise modified compound which has the characteristic chemical structure of a cyclodextrin sufficiently to function as a cyclodextrin component, for example, to enhance the solubility and/or stability of active components and/or reduce unwanted side effects of the active components and/or to form inclusive complexes with active components, as described herein.

Although cyclodextrins and/or their derivatives may be employed as SECs, one embodiment of the invention may include SECs other than cyclodextrins and/or their derivatives.

A particularly useful and preferred class of polyanionic component includes anionic cellulose

derivatives. Anionic cellulose derivatives include metal carboxymethylcelluloses, metal carboxymethylhydroxyethylcelluloses and hydroxypropylmethylcelluloses and derivatives thereof.

The present polyanionic components often can exist in the unionized state, for example, in the solid state, in combination with a companion or counter ion, in particular a plurality of discrete cations equal in number to the number of discrete anionic charges so that the unionized polyanionic component is electrically neutral. For example, the present unionized polyanionic components may be present in the acid form and/or in combination with one or more metals. Since the polyanionic components are preferably ophthalmically acceptable, it is preferred that the metal associated with the unionized polyanionic component be ophthalmically acceptable in the concentrations used. Particularly useful metals include the alkali metals, for example, sodium and potassium, the alkaline earth metals, for example, calcium and magnesium, and mixtures thereof. Sodium is very useful to provide the counter ion in the unionized polyanionic component. Polyanionic components which, in the unionized states, are combined with cations other than H^+ and metal cations can be employed in the present invention.

The amount of SEC in the present compositions is not of critical importance so long as solubility at the alpha-2-adrenergic agonist component is at least somewhat increased and is present in a biologically acceptable amount. Such amount should be effective to perform the desired function or functions in the present composition and/or after administration to the human or animal. In one embodiment, the amount of SEC, preferably the polyanionic component, is sufficient to complex at least in a major amount, and more preferably substantially all,

of the alpha-2-adrenergic agonist component in the present composition. In one useful embodiment, the amount of polyanionic component in the present composition is in the range of about 0.1% to about 30% (w/v) or more of the composition. Preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 10% (w/v). More preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 0.6% (w/v). Even more preferably, the polyanionic component is carboxymethylcellulose and is present in the composition in the range of about 0.2% (w/v) to about 0.6% (w/v). A particularly useful concentration of carboxymethylcellulose in the present compositions is about 0.5%.

In one embodiment, the SECs, for example a carboxymethylcellulose, assist in solubilizing the alpha-2-adrenergic agonist components in the compositions. Although the SECs are capable aiding in the solubilization of ionized alpha-2-adrenergic agonist components, it is preferable that the SECs used in this invention could assist in the solubilization of unionized alpha-2-adrenergic agonist components. For example, in one embodiment, carboxymethylcellulose may help solubilize ionized alpha-2-adrenergic agonist components. In another embodiment, carboxymethylcellulose may help solubilize unionized alpha-2-adrenergic agonist components. In a preferred embodiment, the carboxylmethylcellulose helps solubilize ionized Brimonidine tartrate in the compositions. More preferably, the carboxylmethylcellulose helps solubilize unionized Brimonidine tartrate in the compositions.

In one embodiment, the compositions may also include preservative components or components which assist in the preservation of the composition. The preservative

components selected so as to be effective and efficacious as preservatives in the present compositions, that is in the presence of polyanionic components, and preferably have reduced toxicity and more preferably substantially no toxicity when the compositions are administered to a human or animal.

Preservatives or components which assist in the preservation of the composition which are commonly used in pharmaceutical compositions are often less effective when used in the presence of solubilizing agents. In certain instances, this reduced preservative efficacy can be compensated for by using increased amounts of the preservative. However, where sensitive or delicate body tissue is involved, this approach may not be available since the preservative itself may cause some adverse reaction or sensitivity in the human or animal, to whom the composition is administered.

Preferably, the present preservative components or components which assist in the preservation of the composition, preferably the alpha-2-adrenergic agonist components therein, are effective in concentrations of less than about 1% (w/v) or about 0.8% (w/v) and may be 500 ppm (w/v) or less, for example, in the range of about 10 ppm(w/v) or less to about 200 ppm(w/v). Preservative components in accordance with the present invention preferably include, but are not limited to, those which form complexes with the polyanionic component to a lesser extent than does benzalkonium chloride.

Very useful examples of the present preservative components include, but are not limited to oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof. Specific examples of oxy-chloro components useful as preservatives in accordance with the

present invention include hypochlorite components, for example hypochlorites; chlorate components, for example chlorates; perchlorate components, for example perchlorates; and chlorite components. Examples of chlorite components include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures therefor. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Purite™ by Allergan, Inc. Other examples of oxidative preservative components includes peroxy components. For example, trace amounts of peroxy components stabilized with a hydrogen peroxide stabilizer, such as diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid, may be utilized as a preservative for use in components designed to be used in the ocular environment. Also, virtually any peroxy component may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. Examples of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, may not be stabilized utilizing the present system. See, for example, Martin et al U.S. Patent No.

5,725,887, the disclosure of which is incorporated in its entirety herein by reference.

Preservatives other than oxidative preservative components may be included in the compositions. The choice of preservatives may depend on the route of administration. Preservatives suitable for compositions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic compositions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds and the like known generically as "benzalkonium chloride." For compositions to be administered by inhalation, however, the preferred preservative is chlorbutol and the like. Other preservatives which may be used, especially for compositions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and mixtures thereof, such as the mixture of methyl, ethyl, propyl, butyl esters and the like which is sold under the trade name "Nipastat."

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component, a preservative component in an effective amount to at least aid in preserving , preferably in an amount effective to preserve, the compositions and a liquid carrier component. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which (1) do not substantially or significantly detrimentally affect the alpha-2-adrenergic agonist components in the compositions or the patients to whom the compositions are administered, and (2) are substantially biologically acceptable and chemically stable. Such compositions in accordance with the present invention comprise an alpha-2-

adrenergic agonist component, an oxy-chloro component, and a liquid carrier component, and preferably are substantially free of cyclodextrins.

The carrier components useful in the present invention are selected to be non-toxic and have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. In one embodiment, the carrier component is a liquid carrier. In a preferred embodiment, the carrier component is a liquid aqueous carrier component. A particularly useful aqueous liquid carrier component is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution. The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5. The liquid medium preferably has an ophthalmically acceptable tonicity level, for example, of at least about 200 mOsmol/kg, more preferably in the range of about 200 to about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the carrier component substantially corresponds to the tonicity of the fluids of the eye, in particular the human eye.

In one embodiment, the carrier components containing the SECs and the alpha-2-adrenergic agonist components may have viscosities of more than about 0.01 centipoise (cps) at 25°C, preferably more than about 1 cps at 25°C, even more preferably more than about 10 cps at 25°C. In a preferred embodiment, the composition has a viscosity of about 50 cps at 25°C and comprises a conventional buffer saline solution, a carboxymethylcellulose, and a Brimonidine tartrate.

In order to insure that the pH of the aqueous liquid

carrier component, and thus the pH of the composition, is maintained within the desired range, the aqueous liquid carrier component may include at least one buffer component. Although any suitable buffer component may be employed, it is preferred to select such component so as not to produce a significant amount of chlorine dioxide or evolve significant amounts of gas, such as CO_2. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components are advantageously used in the present invention.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid aqueous carrier component and do not have deleterious or toxic properties which could harm the human or animal to whom the present compositions are administered. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring agents, surface active agents, thickeners, lubricants, and the like, for example, such additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium

carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gun tragacanth and gun acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof. Such aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gun tragacanth, naturally-occurring phosphatides, for example, soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example,

sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

In one broad aspect of the invention, complexes are formed in the present compositions. In one embodiment, the complexes include at least one monomer unit of a quinoxaline component. Examples of quinoxaline components include quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts thereof, esters thereof, other derivatives thereof, and the like and mixtures thereof. For example, in one embodiment, a complex of the present invention may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units. In another embodiment, the complex may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units and Brimonidine tartrate monomer units.

In a preferred embodiment, the complexes of the present invention are dimers. For example, a dimer in accordance with the present invention may include a quinoxaline and a 5-bromo-6-(2-imidozolin-2-ylamino)

quinoxaline. Preferably, a dimer in accordance with the present invention includes two Brimonidine tartrate monomer units.

Without wishing to limit the invention to any theory or mechanism of operation, it is believed that any peroxide forming agent or strong oxidizing agent such as the oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof may facilitate the formation of the complexes, preferably complexes of alpha-2-adrenergic agonist components. For example, dimers of Brimonidine tartrate monomer units are believed to be formed in the presence of chlorites, preferably stabilized chlorine dioxide.

Furthermore, it is believed that the interactions between the monomers which serve to hold the monomers or monomer subunits together to form a complex, preferably an oligomer and more preferably a dimer, may include, but not limited to, covalent bonding, ionic bonding, hydrophobic bonding, electrostatic bonding, hydrogen bonding, other chemical and/or physical interactions, and the like and combinations thereof. Such complexes may disassociate in liquid, for example, aqueous liquid, media. In one embodiment, the monomers or monomer subunits are held together by other than covalent bonding. In one embodiment, the monomers or monomer subunits are held together by electrostatic bonding or forces.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Brimonidine tartrate has a pKa of about 7.78. The pH-solubility profile of 0.5% (w/v) Brimonidine tartrate in a formulation, Ophthalmic Solution, was established in

the pH range of about 5 to about 8 at 23 °C. Table 1. It will be understood that concentrations of adrenergic agonists other than 0.5% may be used, so long as they have therapeutic activity. Likewise, the temperature may be varied, for example, solubility curves may be performed at 37 °C (98.6 °F). The formulation vehicle was prepared by first dissolving polyvinyl alcohol (PVA) in water. The PVA was added to approximately 1/3 of the required total amount of purified water with constant stirring. The slurry was stirred for 20-30 minutes and then heated to 80-95 °C with constant stirring. The mixture was removed from the heat source within 1 hour after having reached the temperature of 80-90 °C and stirred for an additional 10 minutes to ensure homogeneity (Part I). The other ingredients of the Ophthalmic Solution, except for Brimonidine tartrate, were dissolved in a separate container with an additional 1/3 of the required total amount of purified water (Part II). The PVA mixture (Part I) was then quantitatively transferred to Part II using several rinse volumes of purified water. The solution was adjusted to final volume with purified water without pH adjustment.

Brimonidine tartrate was weighed and transferred to a 10 mL test tube containing 5 mL of the formulation vehicle described above. The pH of each sample was then adjusted to a desired value using dilute sodium hydroxide and/or dilute hydrochloric acid. The samples were placed in a rack on a stir plate and stirred at high speed to achieve uniform mixing for 2 days; a partition was placed between the rack and the stir plate to prevent any heat diffusion from the stir plate to the samples. The temperature of the laboratory was monitored throughout the study and was found to be 23±1 °C.

At the end of two days of stirring, the pH value of

each sample was measured, and then approximately 1 mL of each sample was placed in a micro centrifuge tube (polypropylene) and centrifuged at 4,000 rpm for 10 minutes. The supernatant was filtered through a 1μm filter unit (Whatman, 13mm, PTFE). The first 3-4 drops of the filtrate were discarded; the rest of the filtrate was received and diluted quantitatively with HPLC mobile phase. The dilute sample was then injected directly on the HPLC column (Dupont Zorbax, 250mm x 4.6mm, 5μm) for Brimonidine tartrate assay in order to quantify the amount of Brimonidine tartrate. A control of 10.05% Brimonidine tartrate was prepared in the formulation vehicle at pH 6.3-6.5 and assayed before (untreated) and after (treated) centrifugation and filtration. This was done to evaluate the potential loss of Brimonidine tartrate in these two steps of the sample preparation. To ensure reproducibility, the study was repeated on consecutive days.

Table I. 0.5% Brimonidine tartrate in Ophthalmic Solution.

Ingredient	Percent (w/v)
Brimonidine tartrate	0.50
Benzalkonium Chloride, NF	0.0050
Polyvinyl Alcohol, USP	1.4
Sodium Chloride, USP	0.66
Sodium Citrate, Dihydrate, USP	0.45
Hydrochloric Acid, NF or Sodium Hydroxide, NF for pH adjustment	5-8
Purified Water, USP	QS

The solubility data for Brimonidine tartrate in the formulation vehicles are presented in Table II. The results show that the solubility of Brimonidine tartrate

is highly pH-dependent and spans more than two orders of magnitude over the pH range of 5-8. The solubility decreases sharply as the pH increases. The results for the treated and untreated controls are very close, suggesting that centrifugation and filtration does not cause any significant loss of Brimonidine tartrate. The two solubility profiles obtained on consecutive days agree with each other.

Table II. Solubility of Brimonidine tartrate in the Ophthalmic Solution Over pH Range of 5 to 8.

	STUDY 1		STUDY 2	
Sample	pH[a]	Solubility[a]	pH[a]	Solubility[a]
1	5.55	≥164.4[b]	5.50	≥200.6[b]
2	5.92	132.6	5.92	160.8
3	6.14	30.4	6.06	50.1
4	6.57	7.55	6.90	3.19
5	7.00	2.69	7.40	1.19
6	7.45	1.17	7.77	0.63
7	7.83	0.62	7.86	0.58
8	—	—	7.88	0.54
Control/ (untreated)	—	0.486[c]	—	—
Control/ (treated)	—	0.484[d]	—	—

[a] Measured after stirring for two-days before sample withdrawal for centrifugation and filtration.

[b] Represents theoretical concentration based on sample weight. The sample solution was clear indicating that all of the Brimonidine tartrate had dissolved.

[c] Concentration of Brimonidine tartrate in

control before centrifugation and filtration step.

[d] Concentration of Brimonidine tartrate in control after centrifugation and filtration step.

[e] %w/v.

EXAMPLE 2

The pH-solubility profiles of Brimonidine tartrate in compositions (solutions) containing SECs and oxy-chloro components were determined. Particularly, the effects of sodium carboxymethylcellulose (CMC), an SEC, on the solubility of Brimonidine tartrate at various pH conditions were determined. The various concentrations of CMC tested with Brimonidine tartrate were 0%, 0.056%, 0.17%, 0.5%, 1.5% (w/v), Table III.

The samples tested also contained isotonic components, buffer components, and stabilized chlorine dioxide (Purite™), Table III. Sodium carboxymethyl-cellulose, sodium chloride, potassium chloride, calcium chloride dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

Table III

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	
Brimonidine tartrate	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
CMC	0.0%	0.056%	0.17%	0.5%	1.5%	(w/v)
Stabilized chlorine dioxide[a]	0.005%	0.005%	0.005%	0.005%	0.005%	(w/v)
Sodium chloride	0.58%	0.58%	0.58%	0.58%	0.58%	(w/v)
Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)
Calcium chloride, dihydrate	0.02%	0.02%	0.02%	0.02%	0.02%	(w/v)
magnesium chloride, hexahydrate	0.006%	0.006%	0.006%	0.006%	0.006%	(w/v)
boric acid	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
sodium tetraborate, decahydrate	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)

[a] Sold under the trademark Purite™ by Allergan, Inc.

Each sample (1 through 5) was subjected to a range of pH's from about 7 to about 10. The vials containing the sample solutions were placed on a laboratory rotator and left for equilibration for fifteen days at room temperature (~21 °C). The sample solutions were filtered using a 25 mm diameter polysulfone cellulose acetate syringe type filter with 0.45μm pore size. The filtered solutions were assayed for Brimonidine.

Conventional HPLC and detection techniques were used to detect and determine the concentrations of soluble Brimonidine tartrate. Table IV. The solubility is plotted against pH for each CMC concentration. The experimental data points were fitted to a modified Henderson-Hasselbalch equation using a nonlinear least squares routine (Deltagraph version 4.0 DeltaPoint, Inc.), Fig. 1. The R^2 values show the goodness of fit between the experimental values and the theoretical equation to be better than 0.991.

Table IV

	Solubility of Brimonidine tartrate (%)				
	0%CMC	0.056%CMC	0.17%CMC	0.5%CMC	1.5%CMC
pH					
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
7.56				0.1451	
7.68	0.0786				
7.77		0.0721			
7.81			0.0735		
8.10					0.0498
8.46				0.0313	
8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

Fig. 1 clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.056% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.5%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point

what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

EXAMPLE 3

Brimonidine tartrate dimers.

Brimonidine tartrate is added to a test tube containing a composition including chlorite. The test tube was allowed to equilibrate for ten days. Samples obtained from the test tube is analyzed. It is observed that a portion of the Brimonidine tartrate monomer units conjugated to form dimers.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

WHAT IS CLAIMED IS:

1. A composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

a solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component; and

a liquid carrier component.

2. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof and mixtures thereof.

3. The composition of claim 1 wherein the therapeutically active component includes a quinoxaline component.

4. The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.

5. The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and tartrate of 5-bromo-6-(2-imidozolin-2-

ylamino) quinoxaline, derivatives thereof and mixtures thereof.

6. The composition of claim 1 wherein the therapeutically active component comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

7. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is substantially unionized.

8. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is substantially unionized in a biological environment to which the composition is administered.

9. The composition of claim 1 wherein the alpha-2-adrenergic agonist component has increased diffusion through a lipid membrane relative to an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

10. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is selected from the group consisting of agonists of alpha-2A-adrenergic receptors, agonists of alpha-2B-adrenergic receptors, agonists of alpha-2D-adrenergic receptors and mixtures thereof.

11. The composition of claim 1 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to the solubility in a biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

12. The composition of claim 1 wherein the solubility enhancing component comprises a polyanionic component.

13. The composition of claim 12 wherein said polyanionic component is selected from the group consisting of anionic cellulose derivatives, anionic polymers derived from acrylic acid, anionic polymers derived from methacrylic acid, anionic polymers derived from alginic acid, anionic polymers derived from amino acids and mixtures thereof.

14. The composition of claim 1 wherein the solubility enhancing component is selected from the group consisting of anionic cellulose derivatives and mixtures thereof.

15. The composition of claim 1 wherein the solubility enhancing component is selected from the group consisting of carboxymethylcelluloses and derivatives thereof.

16. The composition of claim 1 wherein the solubility enhancing component is present in an amount in a range of about 0.1% (w/v) to about 30% (w/v).

17. The composition of claim 1 wherein the solubility enhancing component is present in an amount in a range of about 0.2% (w/v) to about 10% (w/v).

18. The composition of claim 1 wherein the solubility enhancing component is present in an amount in a range of about 0.2% (w/v) to about 0.6% (w/v).

19. The composition of claim 1 wherein the liquid carrier component is an aqueous liquid carrier component.

20. The composition of claim 1 which is a solution.

21. The composition of claim 1 which has a pH of about 7 or greater.

22. The composition of claim 1 which has a pH in a range of about 7 to about 9.

23. The composition of claim 1 which is ophthalmically acceptable.

24. A composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component; and

an aqueous liquid carrier component.

25. The composition of claim 24 wherein the alpha-2-adrenergic agonist component comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

26. The composition of claim 24 wherein the anionic cellulose derivative comprises carboxymethylcellulose.

27. The composition of claim 24 wherein the anionic cellulose derivative is present in an amount in a range of about 0.2% (w/v) to about 0.6% (w/v).

28. A composition comprising:

a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

a solubility enhancing component in an amount effective to increase the solubility of the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline; and

an aqueous liquid carrier component.

29. The composition of claim 28 wherein the solubility enhancing component comprises a carboxymethylcellulose.

30. The composition of claim 28 which is ophthalmically acceptable.

31. A complex comprising monomer units derived from one or more quinoxaline components.

32. The complex of claim 31 wherein the quinoxaline component is selected from the group consisting of a quinoxaline, a (2-imidozolin-2-ylamino) quinoxaline, a 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, derivatives thereof and mixtures thereof.

33. The complex of claim 31 wherein the quinoxaline component is a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

34. An oligomer comprising monomer units derived from a quinoxaline component.

35. The oligomer of claim 34 wherein the quinoxaline component is selected from the group consisting of a quinoxaline, a (2-imidozolin-2-ylamino) quinoxaline, a 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, derivatives thereof and mixtures thereof.

36. The oligomer of claim 34 wherein the quinoxaline component is a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

37. The oligomer of claim 34 which is a dimer.

38. The oligomer of claim 35 which is a dimer.

39. The oligomer of claim 36 which is a dimer.

40. A composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

an oxy-chloro component in an effective amount to at least aid in preserving the composition; and

a liquid carrier component,

wherein the composition is substantially free of cyclodextrins.

41. The composition of claim 40 wherein the alpha-2-adrenergic agonist component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof and mixtures thereof.

42. The composition of claim 40 wherein the

therapeutically active component includes a quinoxaline component.

43. The composition of claim 42 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.

44. The composition of claim 40 which further includes a solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

45. The composition of claim 44 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to the solubility in a biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

46. The composition of claim 44 wherein the solubility enhancing component comprises a polyanionic component.

Add A2

add R4

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DECLARATION FOR PATENT APPLICATION

D-2892

As a below named inventor, I hereby declare that:

My residence post office address and citizenship are as stated below next to my name.
I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS** the specification of which

(check one) [X] is attached hereto
[ ] was filed on
as US Application Serial Number or PCT International Application Number
and was amended on ___ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification,

including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to the patentability as defined in 37 CFR § 1.56.
I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. **NONE**

Prior Foreign Application(s)			Priority Not Claimed [ ]
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

60/218,200	July 14, 2000
(Application Number)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s), or §365(c) of any PCT International application designation the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application. **NONE**

(Application Number)	(Filing Date)	(Status -patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: **Martin A. Voet, Reg. No. 25,208, Robert Baran, Reg. No. 25,806, Carlos A. Fisher, Reg. No. 36,510, Stephen Donovan, Reg. No. 33,433 and Frank J. Uxa, Reg. No. 25,612**

10236566 .090602

Address all telephone calls to **Frank J. Uxa - Telephone: 949-450-1750**
Address all correspondence to **Frank J. Uxa**
4 Venture, Suite 300
Irvine, CA 92618

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor (given name, family name) **OREST OLEJNIK**

Inventor's signature _____ Date 7/9/01
Residence **Coto de Coza, CA** Citizenship U-SA.
Post Office Address **5 Addington Place**
Coto de Coza, CA 92679

Full name of second inventor (given name, family name) **EDWARD D.S. KERSLAKE**

Inventor's signature _____ Date 7/3/2001
Residence **Charleston, MA** Citizenship ~~U.S.A.~~ U.K
Post Office Address **30 Elm Street, #1**
Charleston, MA 02129

26 MOUNT VERNON
CHARLESTOWN
MA, ~~30~~ 02129

FORM PTO-1595
(Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
OREST OLEJNIK
EDWARD D.S. KERSLAKE

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)
Name: ALLERGAN SALES, INC.
Internal Address: PO BOX 19534

Street Address: 2525 DUPONT DRIVE
IRVINE, CA 92612

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other: _____
Execution Date: JULY 3RD AND 9TH, 2001

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is: JULY 3 & 9, 2001
A. Patent Application No.(s)
B. Patent No. (s)
Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: ALLERGAN, INC.
Internal Address: PO BOX 19534
Street Address: 2525 DUPONT DRIVE
IRVINE, CA 92612

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40
☐ Enclosed
X Authorized to be charged to deposit account

8. Deposit account number: 01-0885
(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

FRANK J. UXA
Name of Person Signing

Signature

July 10, 2001
Date

3
Total number of pages including cover sheet, attachments and document:

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box assignments
Washington, D.C. 20231

10236566 .090602

OLEJNIK ET AL 1 Docket No. 17361(AP)

ASSIGNMENT

WHEREAS we, Orest Olejnik of ORANGE COUNTY, CALIFORNIA and Edward D.S. Kerslake of SUFFOLK COUNTY, MASSACHUSETTS (hereinafter referred to as ASSIGNOR), have invented and own a certain invention entitled: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS for which I have executed a provisional application, and non-provisional application claiming priority thereto, for Letters Patent of the United States, said provisional patent application having been filed July 14, 2000 and bearing Serial No. 60/218,200 and said non-provisional application for which application for Letters Patent of the United States has been executed on even date herewith.

WHEREAS: Allergan Sales, Inc., having its principal place of business at 2525 Dupont Drive, Irvine, CA 92612 (hereinafter referred to as ASSIGNEE), is desirous of acquiring the entire interest in, to and under said invention and in, to and under Letters Patent or similar legal protection to be obtained therefor in the United States and in any and all foreign countries.

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by ASSIGNEE TO ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, ASSIGNOR hereby sells, assigns and transfers to ASSIGNEE the full and exclusive right, title and interest to said invention in the United States and its territorial possessions and in all foreign countries to all Letters Patent or similar legal protection in the United States and its territorial possessions and in any and all foreign countries to be obtained for said invention by said application or any continuation, divisional, renewal, substitute or reissue thereof or any legal equivalent thereof in a foreign country for the full term or terms for which the same may be granted.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent and legal equivalents in foreign countries as may be known and accessible to ASSIGNOR and will testify as to the same in any interference or litigation related thereto and will promptly execute and deliver to ASSIGNEE or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalent thereof in any foreign country which may be necessary or desirable to carry out the purposes thereof.

10236566.090602

OLEJNIK ET AL 2 Docket No. 17361(AP)

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

7/9, 2001.

OREST OLEJNIK

State of CALIFORNIA)
) ss:
County of ORANGE)

On JULY 9, 2001 before me, MARY LOU McNOWN personally appeared OREST OLEJNIK personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/~~are~~ subscribed to the within instrument and acknowledged to me that he/~~she/they~~ executed the same in his/~~her/their~~ authorized capacity(~~ies~~), and that by his/~~her/their~~ signature(s) on the instrument the person, or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

MARY LOU MCNOWN
Commission # 1229524
Notary Public - California
Orange County
My Comm. Expires Aug 16, 2003

Mary Lou McNown
Notary Public

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

7/3, 2001.

EDWARD D.S. KERSLAKE

State of MASSACHUSETTS)
) ss:
County of Suffolk)

On July 3, 2001 before me, Maureen Vibert, Notary Public personally appeared Edward D.S. Kerslake personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person, or the entity upon behalf of which the person(s) acted, executed the instrument.

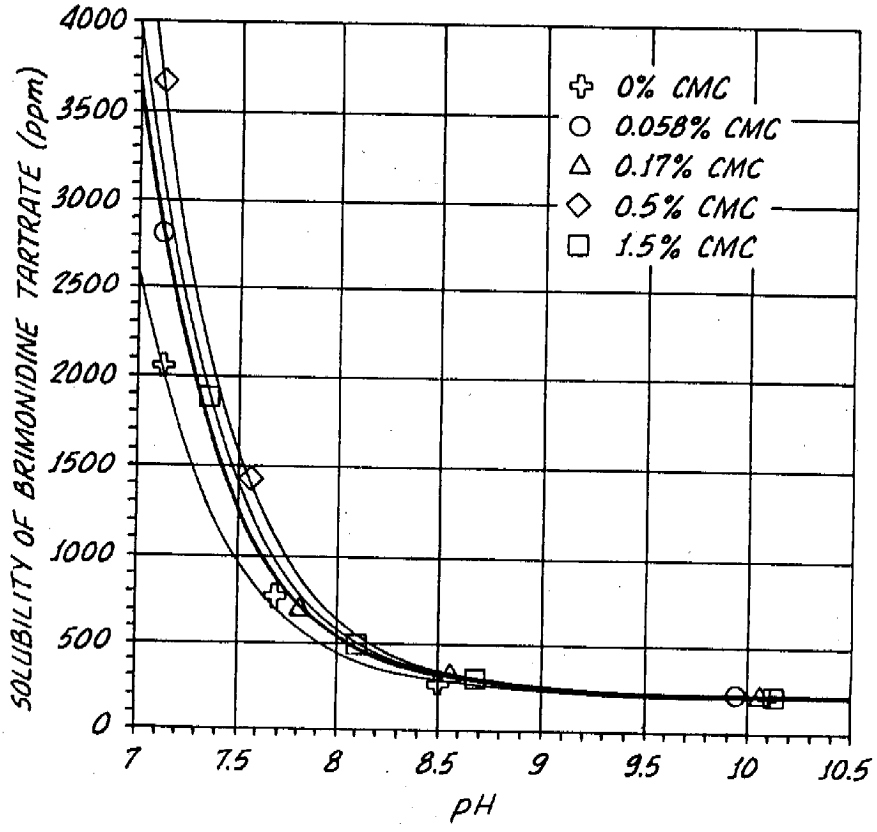
WITNESS my hand and official seal.

Maureen R Vibert
Notary Public
My Commission Expires: 11/6/2006

10236566.090602

PRINT OF DRAWINGS
AS ORIGINALLY FILED

1/1



10236566 .090602

APPLICATION DATA SHEET

Inventor Information

Inventor One Given Name::	Orest
Family Name::	Olejnik
Postal Address Line One::	5 Addington Place
Postal Address Line Two::	
City::	Coto de Coza
State or Province::	CA
Postal or Zip Code::	92679
Citizenship Country::	USA

Inventor Two Given Name::	Edward D.S.
Family Name::	Kerslake
Postal Address Line One::	26 Mount Vernon
Postal Address Line Two::	
City::	Charlestown
State or Province::	MA
Postal or Zip Code::	02129
Citizenship Country::	UK

Correspondence Information

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Name Line Two::	Stout, Uxa, Buyan & Mullins, LLP
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State or Province::	CA
Postal or Zip Code::	92618
Telephone::	949-450-1750
Fax::	949-450-1764
Electronic Mail::	fjuxa@patlawyers.com

10236566 .090602

Application Information

Title Line One::	Compositions Containing Alpha-2-Adrenergic
Title Line Two::	Agonist Components
Total Drawing Sheets::	1
Formal Drawings?::	Yes
Application Type::	Utility

Representative Information

Registration Number One::	Frank J. Uxa, Jr..... 25,612
Registration Number Two::	Donald E. Stout..... 34,493
Registration Number Three::	Robert D. Buyan..... 32,460
Registration Number Four::	Kenton R. Mullins..... 36,331
Registration Number Five::	Jo Anne M. Ybaben..... 42,243
Registration Number Six::	Linda Allyson Fox..... 38,883
Registration Number Seven::	Kyle D. Yesland..... 45,520
Registration Number Eight::	Ketan Vakil..... 43,215
Registration Number Nine::	Greg S. Hollrigel, Ph. D..... 45,374
Registration Number Ten::	Martin A. Voet..... 25,208
Registration Number Eleven::	Robert J. Baran..... 25,806
Registration Number Twelve::	Carlos A. Fisher..... 36,510
Registration Number Thirteen::	Stephen Donovan..... 33,433

Continuity Information

This application is a::	Regular
>Application One::	60/218,200
Filing Date::	July 14, 2000
This application is a::	Continuation
>Application One::	09/904,018
Filing Date::	July 10, 2001

Assignment Information

10236566.090602

Assignee Name::	Allergan Sales, Inc.
Postal Address Line One::	2525 Dupont Drive
Postal Address Line Two::	
City::	Irvine
State or Province::	CA
Postal or Zip Code::	92612

9-9-02 10236566.090602 A

S(S 10/97)

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No
D-2892CON

Total Pages in this Submission

TO THE COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 CFR 1.53(b) is a new utility patent application for an invention entitled:

COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

and invented by:

OLEJNIK ET AL

If a CONTINUATION APPLICATION, *check appropriate box an supply the requisite information:*
[x**Continuation** [ ]**Divisional** [ ]**Continuation-In-part (CIP)** of prior application No.: **09/904,018 filed July 10, 2001, which, in turn , claims the benefit of U.S. Provisional Application Serial No. 60/218,200, filed July 14, 2000.**

Enclosed are **Application Elements**:

[x] Filing Fee

[x] Specification having 40 page(s) and including the following:
- [x] Title of the Invention
- [X] Cross References to Related Applications *(if applicable)*
- [x] Background of the Invention
- [x] Brief Summary of the Invention
- [x] Description of the Drawings
- [x] Detailed Description
- [x] Claim(s) as Classified Below
- [x] Abstract of the Disclosure

[x] 1 Sheets of Drawings(s) (37 CFR 113) [X] Formal [ ] Informal

[x] Oath or Declaration [x] Executed [ ] Unexecuted
[x] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[x] Power of Attorney [x] Executed [ ] Unexecuted
[x] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[ ] Incorporation By Reference -- The entire disclosure of the prior application from which a copy of the oath or declaration is supplied under the above entry, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

[ ] Computer Program in Microfiche *(Appendix)*

Accompanying Application Parts

[x] Assignment Papers (cover sheets & documents(s))
[x] The prior application is assigned of record to **Allergan Sales, Inc.**
[x] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[ ] 37 CFR 3.73(B) Statement *(when there is an assignee)*

10236566.090602

[ ] English Translation Docume *applicable)*
[x] Information Disclosure Statement/PTO-1449 [ ] Copies of _ IDS Cited Reference(s)
[x] Preliminary Amendment
[x] Acknowledgment postcard
[ ] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
[x] Certificate of Mailing by Express Mail
[ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

Fee Calculation and Transmittal

** The filing fee is calculated on the basis of the claims existing in the prior application as amended by the accompanying preliminary amendment noted above.*

CLAIMS AS FILED					
For	**#Filed**	**#Allowed**	**#Extra**	**Rate**	**Fee**
Total Claims	20	- 20 =	0	X $18.00	$0.00
Independent Claims	2	- 3 =	0	X $80.00	$ 0.00
Multiple Dependent Claims *(check if applicable)* [ ]					$ 0.00
				BASIC FEE	$740.00
OTHER FEE *(specify purpose) ASSIGNMENT RECORDATION FEE*					
(Applicant has small entity status under 37 CFR 1.9 and 1.27)				**SMALL ENTITY STATUS**	--
				TOTAL FILING FEE	$740.00

[ ] A check in the amount of $ __ to cover the filing fee and the assignment fee is enclosed.
[x] The Commissioner is hereby authorized to charge and/or credit Deposit Account Number **01-0885** as described below.
  [x] Charge the amount of **$740.00** as filing fee and assignment fee.
  [x] Credit any overpayment.
  [x] Charge any additional filing fees required under 37 CFR 1.16 and 1.17.

Respectfully Submitted,

Frank J. Uxa
Attorney for Applicants
Registration Number: 25,612

Stout, Uxa, Buyan & Mullins, LLP
4 VENTURE, SUITE 300, IRVINE, CA 92618
phone (949) 450-1750; *fax* (949) 450-1764

10235566.090602

#2/A
11/1/02

D-2892CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT

In the application of:
Olejnik et al

Group Art Unit: N/A

Serial No. N/A

Examiner: N/A

Filing Date: HEREWITH

For: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, DC 20231

Dear Sir:

Please amend the subject application as follows:

IN THE SPECIFICATION

Page 1, delete the first paragraph and insert in place thereof:

A1 --This application is a continuation of application Serial No. 09/904,018, filed July 10, 2001 which, in turn, claims the benefit of U.S. Provisional Application Serial No. 60/218,200, filed July 14, 2002. The disclosure of each of the above-noted applications is incorporated in its entirety herein by reference.--

IN THE CLAIMS

Cancel Claims 1 to 46, without prejudice.

Add new claims 47 to 66 as follows:

A2 Sub R1 47. (New Claim) A composition comprising;

water; and

up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate being soluble in the composition at 21°C.

48. (New Claim) The composition of claim 47 which includes up to 0.15%(w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

49. (New Claim) The composition of claim 47 which includes about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

50. (New Claim) The composition of claim 47 which includes 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

51. (New Claim) The composition of claim 47 having a pH of 7.0 or greater.

52. (New Claim) The composition of claim 47 which is ophthalmically acceptable.

53. (New Claim) The composition of claim 47 which further comprises an oxy-chloro component in an amount effective to at least assist in preserving the composition.

54. (New Claim) The composition of claim 53 wherein the oxy-chloro component comprises a chlorite component.

55. (New Claim) The composition of claim 47 which is

substantially free of anionic cellulosic derivatives.

9 56. (New Claim) The composition of claim 47 which is substantially free of carboxymethyl cellulose.

AP cont'd

57. (New Claim) A composition comprising:
water; and
up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the composition at 21°C.

Sub B3

11 58. (New Claim) The composition of claim 57 which includes up to 0.15% (w/v) of the component.

12 59. (New Claim) The composition of claim 57 which includes about 0.15% (w/v) of the component.

13 60. (New Claim) The composition of claim 57 which includes 0.15% (w/v) of the component.

14 61. (New Claim) The composition of claim 57 having a pH of 7.0 or greater.

7 C 62. (New Claim) The composition of claim 57 which is ophthalmically acceptable.

15 63. (New Claim) The composition of claim 57 which further comprises an oxy-chloro component in an amount effective to at least assist in preserving the composition.

10236566.090602

D-2892CON
Olejnik et al
Page 4

14 ~~64~~. (New Claim) The composition of claim ~~63~~ 15 wherein the oxychloro component comprises a chlorite component.

A2 cont'd

15 ~~65~~. (New Claim) The composition of claim ~~51~~ 10 which is substantially free of anionic cellulosic derivatives.

16 ~~66~~. (New Claim) The composition of claim ~~51~~ 10 which is substantially free of carboxymethyl cellulose.

REMARKS

The specification has been amended to make reference to prior, related applications.

Claims 1 to 46 have been canceled, without prejudice.

New claims 47 to 66 have been added and are directed to embodiments for which patent protection is sought. Each of these new claims is fully supported by the present specification.

Applicant respectfully requests early and favorable action in the above-identified application.

Respectfully submitted,

Frank J. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (949) 450-1764

FJUxa/jm

A

#3

D D-2892CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT

In the application of:
Olejnik et al

Group Art Unit: N/A

Serial No. N/A

Examiner: N/A

Filing Date: HEREWITH

For: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

Applicant wishes to call to the attention of the Examiner the documents cited on the accompanying Form PTO-1449. No concession is made that these documents are prior art, and applicant expressly reserves the right to antedate the documents as may be appropriate. Applicant requests that each of these documents be made of record in the above-identified application.

Some of these documents were cited in related application Application Serial No. 09/904,018, filed July 10, 2001 and Application Serial No. 09/903,962, filed July 10, 2001.

Therefore, no copies of these documents are submitted herewith.

Respectfully submitted,

Frank J. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (949) 450-1764

FJUxa/au

DOCKET NO.: D-2892CON

THE ENCLOSED PATENT APPLICATION OF OLEJNIK ET AL IS BEING FILED IN ACCORDANCE WITH SECTION 37 CFR 1.10 BY EXPRESS MAIL AND SHOULD BE ACCORDED A FILING DATE OF:

September 6, 2002

SEE THE EXPRESS MAIL CERTIFICATE ATTACHED TO THE APPLICATION.

Sheet 1 of 1

Form PTO-1449

INFORMATION DISCLOSURE CITATION IN AN APPLICATION
(Use several sheets if necessary)

DOCKET NO: D-2892CON | APPLN. NO.: N/A
APPLICANT: Olejnik et al
FILING DATE: Herewith | GROUP ART: N/A

JC19 U.S. PTO 10/236566 09/06/02

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	RULING DATE
RB	3 2 7 8 4 4 7	10/11/66	McNicholas			
	3 8 9 0 3 1 9	06/17/75	Danielwicz et al.			
	4 5 3 0 9 2 0	07/23/85	Nestor et al.			
	4 8 0 6 5 5 6	02/21/89	Portoghese			
	5 0 2 1 4 1 6	06/04/91	Gluchowski			
	5 2 0 2 1 2 8	04/13/93	Morella et al.			
	5 3 5 2 7 9 6	10/04/94	Hoeger et al.			
	5 4 5 9 1 3 3	10/17/95	Neufeld			
	5 7 0 3 0 7 7	12/30/97	Burke et al.			
	5 7 1 9 1 9 7	02/17/98	Kanios et al.			
	5 7 2 5 8 8 7	03/10/98	Martin et al.			
	5 8 1 4 6 3 8	09/29/98	Lee et al.			
	5 8 3 4 5 0 2	11/10/98	Cheng et al.			
RB	5 9 9 4 1 1 0	11/30/99	Mosbach et al.			

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
RB	2 0 4 8 3 1 5	02/09/92	Canada				
	0 6 0 9 9 6 1	08/10/94	European				
	94 / 1 6 6 8 5	08/04/94	~~International~~ WIPO				
	98 / 4 7 8 7 8	10/29/98	~~International~~ WIPO				
	99 / 4 3 2 9 9	09/02/99	~~International~~ WIPO				
	99 / 5 1 2 7 3	10/14/99	~~International~~ WIPO				
	00 / 1 2 1 3 7	03/09/00	~~International~~ WIPO				
RM	00 / 1 9 9 8 1	04/13/00	~~International~~ WIPO				

OTHER DOCUMENTS

RB	U.S. Patent Application Serial No. 09/903,962, filed July 10, 2001

EXAMINER: Rachel M. Bennett
DATE CONSIDERED: 12/10/02

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/236,566	09/06/2002	Orest Olejnik	D-2892CON	3779

33197 7590 12/18/2002

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618

EXAMINER
BENNETT, RACHEL M

ART UNIT	PAPER NUMBER
1615	4

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	10/236,566	OLEJNIK ET AL.	
	Examiner	Art Unit	
	Rachel M. Bennett	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

U.S. Patent and Trademark Office
PTO-326 (Rev. 04-01) **Office Action Summary** Part of Paper No. 4

DETAILED ACTION

The examiner acknowledges receipt of Preliminary Amendment A and IDS filed 9/6/02.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 47-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 24-30, 40-43 of copending Application No. 09/904,018. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a composition comprising 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline tartate and 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an ophthalmically acceptable formulation comprising an oxy-chloro component while Application 09/904,018 claims a composition comprising a tartate of 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered and an aqueous liquid carrier component. More generally, application 09/904,018 claims a composition comprising an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; an oxy-chloro component in an effective

amount to at least aid in preserving the composition; and a liquid carrier component, wherein the composition is substantially free of cyclodextrins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Claims 47-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35-52 of copending Application No.09/903962. Although the conflicting claims are not identical, they are not patentably distinct from each other because the because the instant claims are drawn to a composition comprising 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline tartate and 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an ophthalmically acceptable formulation comprising and oxy-chloro component while Application 09/903,962 claims a composition comprising a tartate of 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an amount effective to provide a trerapeutic benefit to a patient to whom the composition is administered, a cholorite component in an effective amount to at least aid in preserving the composition and an aqueous liquid carrier component. More generally, application 09/903962 claims a composition comprising an therapeutically active component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; an oxy-chloro component in an effective amount to at least aid in preserving the composition; and a liquid carrier component, wherein the composition is substantially free of cyclodextrins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 47-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burke (US 5215991).

Burke discloses pharmaceutical compositions of alpha 2 agonists and Na+/H+ exchange inhibitors which are useful in lowering intraocular pressure (IOP) and treatment of intraocular hypertension (see abstract). Preferred imidazoline-derived alpha 2 agonists or pharmaceutically acceptable salts thereof are disclosed in col. 3 (see formula). The most preferred imidazoline-derived alpha 2 agonist compounds include 5-bromo-6-(2-imidazolidine-2-ylamino)quinoaxaline. Doses of alpha 2 agonist in an ophthalmic preparation effective, non-toxic amount of the agonist in a pharmaceutically acceptable liquid, gel, cream or aqueous or nonaqueous liquid suspension or solution are preferably from about 0.001% to about 1.0% weight/volume. Regardless of the preferred range stated herein, one can determine the most efficacious dose for a particular alpha 2 agonist by carrying out a dose response curve as is well known in the art (see col. 4 lines 34-44). Various buffers and means for adjusting pH may be used as long as the resulting preparation is ophthalmically acceptable. Benzalkonium choride may be used as a preservative. Burke does not disclose the preservative to be a chlorite component.

Beck discloses compositions including a liquid medium, a cylodextrin component and a preservative component which has a reduced tendency of being complexed with the cyclodextrin component. In one embodiment, the preservative component is a chlorite component. Active compounds, such as pharmaceutically active components or drugs, preferably are included in the compositions (see abstracts). For example, the present compositions may include a pharmaceutically effective in providing a therapeutic effect when administered to the eyes of a human or animal. The preservative employed is preferably ophthalmically acceptable at the concentration employed so that the human or animal is effectively treated without significant harm caused by the presence of the preservative (see col. 1). Preferably, the preservative component has in increased or greater preservative efficacy in the composition relative to an identical amount (w/v) of benzalkonium chloride.

Absent unexpected results, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Burke by substituting the preservative, chlorite as taught by Beck for the benzalkonium choride because of the expectation of increased or greater preservative efficacy as taught by Beck.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel M. Bennett whose telephone number is (703) 308-8779. The examiner can normally be reached on Monday through Friday, 8:00 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (703) 308-2927. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

R. Bennett
December 10, 2002

CARLOS AZPURU
PRIMARY EXAMINER
GROUP 1500

Notice of References Cited	Application/Control No. 10/236,566	Applicant(s)/Patent Under Reexamination OLEJNIK ET AL.	
	Examiner Rachel M. Bennett	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-US006358935B1	03-2002	Beck et al.	514/58
	B	US-US005215991A	06-1993	Burke	514/255
	C	US-US 20020071874A1	06-2002	Olejnik et al.	424/661
	D	US-US 2002/0032201A1	03-2002	Olejnik et al.	514/249
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/236,566	09/06/2002	Orest Olejnik	D-2892CON	3779

33197 7590 03/03/2003

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618

EXAMINER	
BENNETT, RACHEL M	

ART UNIT	PAPER NUMBER
1615	5

DATE MAILED: 03/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Interview Summary	Application No.	Applicant(s)	
	10/236,566	OLEJNIK ET AL.	
	Examiner	Art Unit	
	Rachel M. Bennett	1615	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Rachel M. Bennett*. (3)_____.

(2) *Carlos A. Fisher*. (4)_____.

Date of Interview: *25 February 2003* .

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____ .

Claim(s) discussed: *all pending claims* .

Identification of prior art discussed: *Burke (US 5215991)* .

Agreement with respect to the claims f)☒ somewhat was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The attorney explained the advantages of the composition comprising up to about 0.15%(w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline tartate, wherein the composition has a pH of about 7.0 or greater were unexpected. The attorney agreed to file a declaration showing the unexpected results. Furthermore, the attorney agreed to file a Terminal Disclaimer when allowable subject matter is indicated in the instant application*
.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i)☐ It is not necessary for applicant to provide a separate record of the substance of the interview(if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Rachel Bennett

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check the appropriate box at the bottom of the Form which informs the applicant that the submission of a separate record of the substance of the interview as a supplement to the Form is not required.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

DRAFT CLAIMS: FOR DISCUSSION PURPOSES ONLY
SERIAL NO. 10/236,566
GROUP ART UNIT 1615 EXAMINER BENNETT

47. (Amended) A therapeutically effective aqueous ophthalmic composition comprising:
~~water; and~~
up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at 21°C.

48-52 Original Claims

53. (Amended) The composition of claim 47 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

54-56 Original Claims

57. (Amended) A therapeutically effective aqueous ophthalmic composition comprising:
~~water; and~~
up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the compositon at 21°C.

58-66 Original Claims

67. (New) The composition of claim 53 in which the preservative comprises BAK.

68. (New) The composition of claim 57 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

69. (New) The composition of claim 68 in which the preservative comprises BAK.

70. (New) The composition of claim 68 inm ,which the preservative comprises a oxy-chloro component.

DRAFT CLAIMS
DO NOT
ENTER

Feb-24-03 08:28pm From-ALLERGAN LEGAL DEPARTMENT +17142464249 T-378 P.01/07 F-220

FACSIMILE TRANSMISSION

FROM: **Carlos A. Fisher**
ALLERGAN, Inc.
P.O. Box 19534
2525 Dupont Drive
Irvine, CA 92623-9534

Phone No.: 714-246-4920
Facsimile No.: 714-246-4249

TO: **The United States Patent and Trademark Office**
Assignment Division, **Attention: Examiner Rachael Bennett**
Facsimile No.: 703-746-5315

Number of pages (including this cover page): 7

Please acknowledge receipt of all pages indicated above by faxing this page back to Allergan, Inc at the facsimile number provided above

In re Application of: Olejink et al.

Serial No.: 09904,018 and 10/236,566

Examiner: Rachael Bennett

Date: February 24, 2003

Examiner Bennett,

Cotransmitted please find two sets of draft claims for discussion during our tele[phonic interview; one each for the two above referenced patent applications. I look forward to speaking with you at 8:30 PST.

Best wishes,

Carlos Fisher
Reg. 36, 510

Received from <+17142464249> at 2/24/03 8:28:58 PM [Eastern Standard Time]

DOCKET NO. [illegible]1CON(A) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.	Group Art Unit: 1615
Serial No: 10/236,566	Examiner: Bennett, R.
Filed: September 6, 2002	
For: COMPOSITIONS CONTAINING ALPHA-2-ADRNERGIC AGONIST COMPONENTS	

REPLY TO OFFICE ACTION

This communication is in Reply to the Office Action mailed December 18, 2001. Applicants have carefully studied the Office Action, and respectfully request reconsideration of the claim rejections in light of the claim amendments and comments which follow.

AMENDMENTS TO THE CLAIMS

Kindly make the following amendments to the claims:

47. (Amended) A therapeutically effective aqueous ophthalmic composition comprising:
~~water; and~~
up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at about 21°C.

48-52 Original Claims

53. (Amended) The composition of claim 47 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

54-56 Original Claims

57. (Amended) A therapeutically effective aqueous ophthalmic composition comprising:
~~water; and~~
up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the composition at about 21°C.

58-66 Original Claims

67. (New) The composition of claim 53 in which the preservative comprises benzalkonium chloride.

68. (New) The composition of claim 57 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

69. (New) The composition of claim 68 in which the preservative comprises benzalkonium chloride.

70. (New) The composition of claim 68 in, which the preservative comprises a oxy-chloro component.

REMARKS

Applicants would like to thank Examiner Bennett for her courtesy in granting and conducting a telephonic interview on February 25, 2003. During the interview Examiner Bennett and the undersigned discussed the outstanding rejections and proposed claim amendments.

Independent claims 47 and 57 and dependent claim 53 have been amended, and new claims 67-70 added. All the amendments are supported by the specification. Claims 47 and 57 were amended to indicate that what is being claimed is a therapeutically effective aqueous ophthalmic composition. Support for this amendment can be found, e.g., at page 1, lines 15-16 and page3-7. Claim 52 was amended to add a Markush group of preservative components including oxy-chloro compounds and quaternary ammonium compounds; see pages 18-20. The new claims provide specific embodiments of the invention.

Applicants would like to point out that these claim amendments and cancellations have been made solely in order to enable early allowance of certain aspects of the invention; Applicants have amended claims in this application with the understanding that they may reserve the right to present the unamended versions thereof in a subsequent patent application.

Provisional Double Patenting

The Examiner has made a provisional double patenting rejection of the invention claimed in this patent application over co-pending patent application Serial No. 09/904,018. Applicants are herewith filing a Terminal Disclaimer over the '018 application; thus Applicant believe this rejection is now moot

35 USC §103

The Examiner rejected claims 47-66 as being unpatentable pursuant to 35 USC §103 over Burke (US 5,215,991). Although not explicitly stated, Applicants infer that this rejection is in view of Beck (US Patent 6,358,935), since the discussion mentions the Beck patent. If Applicants are in error, correction is respectfully sought. The Examiner has stated that Burke discloses brimonidine (5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline) in various formulations and concentrations, including an aqueous formulation; the Examiner also states that Beck discloses cyclodextrin-containing compositions containing an oxy-chloro component. The Examiner argues that the currently claimed invention is the result of routine optimization of the conditions cited in Burke. Moreover, the Examiner has cited Beck for the disclosure of oxy-chloro preservatives therein, notwithstanding these preservatives are disclosed as for use with cyclodextrins, which not elements of the compositions presently claimed. Applicants respectfully traverse this rejection for the following reasons.

The current claims are directed to therapeutically effective aqueous ophthalmic compositions comprising brimonidine and salts and esters thereof at a pH of up to about 7.0, and in a concentration of about 0.15% or less. Other claims indicate that the composition is preserved using a quaternary ammonium preservative or an oxychloro preservative.

To appreciate the surprising aspects of the present invention it is important to understand that previous brimonidine solutions for ophthalmic use have been formulated at a pH of about 6.3 – 6.5 and a concentration of 0.2% (w/v). This formulation was approved for marketing in the United States and foreign countries under the trade name Alphagan® .

The present invention is the result of the surprising finding that increasing the pH of a brimonidine solution to a pH of greater than about 7.0 leads to similar efficacy at a 25% lower concentration (from 0.2% (w/v) to about 0.15% (w/v) or less) than is seen in a brimonidine solution at a pH of about 6.6-6.8. This appears to be due to the fact that at a pH closer to the pKa of brimonidine (which has a pKa of about 7.4) than pH 6.3-6.5, a larger proportion of the molecules are electrostatically neutral, and thus less lipophobic than the polarized molecule. As such, a greater amount of the active drug is able to enter the cornea of the eye at a given solution concentration; this effect counters the effects of decreased brimonidine solubility at the higher pH. See specification at e.g., paragraph bridging pages 1 and 2.

However, it is particularly surprising that such a therapeutically effective dosage of brimonidine could be formulated in aqueous solution at a pH greater than about 7.0. Figure 1 of the present specification shows that brimonidine's solubility decreases precipitously at pH values above 7.0. The fact that a therapeutically effective dosage could be provided by a composition containing about 0.15% or less of brimonidine at such pH values is truly unexpected.

For the Examiner's convenience, Applicants hereby attach a copy of an article Katz, et al., *J. Glaucoma* 11:119 (April 2002) which shows the comparison of the 0.2% brimonidine formulation having a pH 6.3-6.5 (the "0.2% formulation") with 0.15% brimonidine solution at pH 7.2 (the 0.15% formulation).

Although the Katz paper does not disclose the pH of either solution, Applicants hereby enclose a Declaration of Amy Batoosingh, Director of Ophthalmological Clinical Research at Allergan, Inc. Ms. Batoosingh, whose work is contained within and acknowledged on page 126 of Katz, indicates in her Declaration that the formulation called "brimonidine 0.2%" in the Katz paper, which used benzalkonium chloride as a preservative, comprised 0.2% brimonidine at pH 6.3-6.5, and that the formulation termed "brimonidine-Purite 0.15%" in Katz, (which used oxy-chloro as a preservative) comprised 0.15% brimonidine at pH 7.2.

As can be seen in Figure 1 on page 122 of Katz, topical application of the 0.15% formulation resulted in no statistically significant differences in its ability to lower intraocular pressure (IOP) compared to the 0.2% formulation, despite 25% less active agent in the former formulation. Thus,

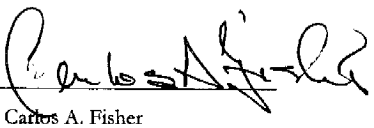
lowering the concentration, when the pH is above about 7.0 unexpectedly had no significant effect on therapeutic efficacy, when compared to the 0.2% formulation.

The advantages of this invention are manifest. Among others, it can be seen that although ophthalmic hypotensive therapeutic efficacy of the 0.15% solution is the same as for the 0.2% solution, the reduced concentration (and thus the reduced dosage) results in a lower potential for systemic side effects, which are typically caused by drainage of topically applied drugs from the eye to the stomach through the nasolacrimal duct. Although brimonidine's side effects are not as severe as some other glaucoma medications, they can still include sedation, hypotension, and reduction in heat rate in some patients. A reduction in the dosage by 25% reduces the likelihood and severity of such side-effects.

Thus, the present invention is drawn to surprising new therapeutic compositions comprising at least a 25% lower concentration of brimonidine than previous ophthalmic formulations, at pH closer both to the solubility limits of brimonidine, and to the pKa of the compound.

For this reason it can be seen that these results were completely unforeseen and surprising, and could therefore not have been anticipated by a person of skill in the art. For this reason, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection, and ask the Examiner to permit the claims to proceed to issue. Should there be any fee in connection with this communication, the Director is authorized to use the Applicants' Deposit Account 01-0885 for the payment of such fees.

Respectfully submitted,

By: 

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DOCKET NO. 17361CON(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.

Serial No: 10/236,566
Conf. No.: 3779
Filed: September 6, 2002

For: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

Group Art Unit: 1626

Examiner: Bennett, R.

TRANSMITTAL SHEET

Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

Transmitted herewith is an Amendment in the above-identified application. Enclosed are:

1) Return/Stamped Postcard
2) Transmittal Sheet
3) Reply and Amendment (5 pgs.)
4) Terminal Disclaimer
5) Declaration of Amy Batoosingh, B.A.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box Amendment-Fee; Assistant Commissioner for Patents, Washington, D.C. 20231 on

3/17/2003 (Date of Deposit)

BONNIE FERGUSON Name of person mailing correspondence

3/17/2003 Date of Signature

Bonnie Ferguson Signature

Serial No. 10/236,560 2 Docket No. 17361CON(AP)

The fee has been calculated as shown below:

CLAIMS AS FILED

	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE
Total Claims	24	20	= 4 ×	$18	= $72.00
Independent Claims	2	2	= 0 ×	$84	= $0.00
If application has been amended to contain multiple dependent claim(s), then add			No	$280	= $0.00
(Select only one) Time Extension Fees:			one month	$110	= $
			two months	$410	= $
			three months	$930	= $
			four months	$1,450	= $
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT		$72.00

( ) A check in the amount of $* is enclosed (place fee in here i.e., petition, excess claims, etc.)

(x) The Commissioner is hereby authorized to charge fees under 37 CFR 1.16 and 1.17 (associated with petition fees or excess claim fees) which may be required, or credit any overpayment to Deposit Account No. 01-0885. A duplicate copy of this sheet is enclosed.

Respectfully Submitted,

Date: 3/17/08

Signature: _____

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DOCKET NO. 17361COMAPP
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.	Group Art Unit: 1626
Serial No: 10/236,566	Examiner: Bennett, R.
Filed: September 6, 2002	
For: COMPOSITIONS CONTAINING ALPHA-2-ADRNERGIC AGONIST COMPONENTS	

DECLARATION OF AMY BATOOSINGH

Dear Sir,

I, Amy Batoosingh, B.A., hereby declare as follows:

1. I hold the title of Director, Ophthalmological Clinical Research at Allergan, Inc. I have worked in the Department of Clinical Research at Allergan for over 20 years.

2. I am a co-author of the article, Katz, et al., *J. Glaucoma* 11:119 (April 2002), entitled *Twelve-Month Evaluation of Brimonidine Purite Versus Brimonidine in Patients with Glaucoma or Ocular Hypertension*, and am familiar with the studies referenced therein.

3. The compositions called "brimonidine 0.2%" and "brimonidine-Purite 0.15%" in the Katz article comprised 0.2% (w/v) brimonidine at pH 6.3-6.5, and 0.15% brimonidine at pH 7.1-7.3, respectively.

4. The conclusion reached as a result of the studies referenced in the Katz et al., article was that brimonidine 0.2% and brimonidine-Purite 0.15% showed comparable efficacy when each was used for the treatment of ocular hypertension in glaucoma and/or ocular hypertensive human patients over a 12 month period of time, despite a significant reduction in the concentration of the active ingredient in the latter formulation.

5. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Sincerely yours,

Amy Batoosingh, B.A.

J Glaucoma 2002
Apr;11(2):119-126

2002050756

Twelve-Month Evaluation of Brimonidine-Purite Versus Brimonidine in Patients With Glaucoma or Ocular Hypertension

L. Jay Katz, MD

Brimonidine-Purite Study Groups 1 and 2, Wills Eye Hospital, Philadelphia, Pennsylvania

Purpose: To compare the efficacy and safety of brimonidine-Purite (Alphagan; Allergan, Irvine, CA) 0.15% and 0.2% three times daily with brimonidine (Alphagan) 0.2% three times daily in patients with glaucoma or ocular hypertension.

Patients and Methods: In this 12-month, randomized, multicenter, double-masked, parallel-group study, patients were randomly assigned to receive brimonidine-Purite 0.15% (n = 381), brimonidine-Purite 0.2% (n = 383), or brimonidine 0.2% (n = 383) three times daily. Visits were conducted before the study, at baseline, at weeks 2 and 6, and at months 3, 6, 9, and 12. Diurnal intraocular pressure was measured at 8 AM, 10 AM, 3 PM, and 5 PM at baseline, week 6, and at months 3, 6, and 12. Intraocular pressure was also measured at 8 and 10 AM at week 2 and month 9. Safety was evaluated by adverse events and other ocular and systemic measures.

Results: At baseline, mean intraocular pressure was similar in the three treatment groups. During follow-up, there were no statistically significant among-group differences in mean intraocular pressure or mean changes from baseline intraocular pressure (at peak or trough). The difference in mean intraocular pressure between the brimonidine-Purite-0.15% and brimonidine-0.2% treatment group was less than 1 mm Hg at all time points. The relative percent difference in allergic conjunctivitis was 41% lower in the brimonidine-Purite 0.15% group compared with the brimonidine 0.2% group. The comfort and satisfaction rating significantly favored brimonidine-Purite 0.15%.

Conclusions: Over 12-months, brimonidine-Purite 0.15% and 0.2% provided intraocular pressure lowering comparable with brimonidine 0.2% in patients with glaucoma or ocular hypertension. Brimonidine-Purite 0.15% showed the most favorable safety and tolerability profile with a reduced incidence of allergic conjunctivitis and better satisfaction and comfort rating.

Key Words: Benzalkonium chloride—Brimonidine—Glaucoma—Ocular hypertension—Purite.

Since the introduction of brimonidine 0.2% ophthalmic solution (Alphagan; Allergan, Irvine, CA) in 1996, this highly selective α_2-adrenergic agonist has proven to be an effective and safe agent for the long-term management of glaucoma and ocular hypertension.[1] In a randomized, continuous clinical trial, the efficacy of brimonidine 0.2% twice daily was sustained over 4 years and was comparable with the efficacy of timolol 0.5%.[2–6] Additional studies have shown the flexibility of brimonidine 0.2% twice daily as an effective monotherapy, adjunctive, and replacement therapy.[7–9] Brimonidine 0.2% twice daily has become a widely accepted first- and second-line therapy for the long-term management of glaucoma and ocular hypertension.

Studies show that brimonidine 0.2% has a lower risk of systemic adverse events than topical β-blockers.[2,3,7,10,11] In addition, brimonidine 0.2% has a lower

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Members of the Brimonidine-Purite Study Groups 1 and 2 are listed in the Appendix at the end of this article.
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incidence of ocular allergy and shows no cross toxicity compared with apraclonidine (Iopidine; Alcon, Fort Worth, TX).[12] Reports of ocular allergy associated with chronic brimonidine therapy range from 4.2% to 12.7% of patients, depending on the diagnostic criteria and duration of therapy.[1,4,13]

A new formulation of brimonidine ophthalmic solution has been developed to enhance safety and tolerability while maintaining effective intraocular pressure (IOP) reduction. Brimonidine-Purite (Alphagan, Allergan, Irvine, CA) has a different preservative and a lower concentration of active drug than the original brimonidine 0.2% (Alphagan). In the reformulation, the preservative has been changed from benzalkonium chloride (BAK) to Purite. Benzalkonium chloride is the most common antimicrobial preservative used in topical multiuse ophthalmic preparations, including most glaucoma medications.[14,15] It works by denaturing proteins, lysing cytoplasmic membranes, and oxidizing enzymes. At high concentrations, BAK may be more toxic than other preservatives. It can accumulate and remain in ocular tissue for relatively lengthy periods, and may induce cell death in a dose-dependent manner.[16,17] Because glaucoma is a chronic disease and patients may be taking multiple glaucoma medications, these patients may be exposed to high concentrations of BAK with potentially detrimental ocular effects. In contrast, Purite is a stabilized oxychloro complex and oxidative preservative used in Refresh Tears (Allergan, Irvine, CA) artificial eye lubricant and Lens Plus Purite (Allergan, Irvine, CA) Saline.[18–20] When Purite is exposed to light, it is converted to natural tear components (i.e., sodium and chloride ions, oxygen, and water).[21] Purite is a microbicide with a wide spectrum of antimicrobial activity and a very low level of toxicity in mammalian cells.[22]

In addition to the change in preservative, brimonidine-Purite 0.15% contains 25% less active drug than original brimonidine 0.2%. Animal studies suggest that brimonidine tartrate has enhanced ocular bioavailability when formulated as brimonidine-Purite.[23] In addition, 0.15% is the lowest effective concentration tested, which attains the desired therapeutic effect.[24] Therefore, the new formulation of brimonidine may provide an improved safety and tolerability profile with comparable efficacy.

The objective of this study was to evaluate the safety and efficacy of brimonidine-Purite 0.15% and 0.2% compared with brimonidine 0.2%. The results represent the pooled analyses of two identically designed clinical trials. All three study medications were administered three times daily for 1 year in patients with glaucoma or ocular hypertension. Although brimonidine twice daily has been shown to be as effective as three-times-daily brimonidine,[24,25] the three-times-a-day dosage was selected for this study to satisfy US regulatory requirements.

PATIENTS AND METHODS

Study Design

Two identically designed, 12-month, double-masked, randomized, parallel-group studies were conducted at 44 sites across the United States. The results presented here are from the analyses of pooled data from these two clinical trials. The studies were conducted in accordance with Institutional Review Board and Informed Consent Regulations. Each investigator obtained appropriate review board approval before study initiation. All patients gave their written consent before participating in any study-related activities. Patients who were treated with ocular hypotensive medications before study entry were required to undergo a washout period ranging from 4 to 28 days, depending on the medication taken. This washout eliminated any potential residual effects of previous therapy.

Patients were randomly assigned to receive brimonidine-Purite 0.15% (n = 381), brimonidine-Purite 0.2% (n = 383), brimonidine 0.2% (n = 383) three times daily in the morning (7:30–8:30 AM), in the mid-afternoon (2:30–3:30 PM), and in the evening (9:30–10:30 PM). Scheduled visits occurred before study, at baseline, at weeks 2 and 6, and at months 3, 6, 9, and 12.

Criteria

Key inclusion criteria included an age of 18 years or older with a diagnosis of glaucoma (primary open angle, pseudoexfoliative, pigment dispersion, chronic angle closure with a patent peripheral iridectomy/iridotomy for at least 3 months) or ocular hypertension (IOP $\geq$ 22 mm Hg, $\leq$ 34 mm Hg in each eye after washout, with between-eye IOP asymmetry $\leq$ 5 mm Hg), likelihood to be controlled on monotherapy, negative pregnancy test for women of childbearing potential, and best corrected visual acuity of 20/100 or better.

Key exclusion criteria included uncontrolled systemic disease, other active ocular disease, abnormally low or high blood pressure or heart rate, anticipated alteration of existing chronic therapy with agents that could substantially affect IOP, use of ocular medication other than periodic use of artificial tears, and functionally significant visual field loss.

Efficacy Variables

The primary efficacy variable was IOP. Diurnal IOP was measured at approximately 8 AM (before the morning drop), 10 AM, 3 PM (before the afternoon drop), and 5 PM at baseline, week 6, and at months 3, 6, and 12. The IOP was also measured at approximately 8 AM (before the morning drop) and 10 AM at week 2 and month 9.

Other efficacy variables included clinical success as evaluated by the investigator (regardless of whether a physician recommended continuation of study medication for the patient), subject satisfaction evaluation, and subject comfort evaluation using standardized scales.

Other measures that were evaluated included adverse events, visual acuity, cup/disc ratio, biomicroscopy, ophthalmoscopy, visual fields, heart rate, and systolic and diastolic blood pressure. The severity of adverse events was assessed based on the following guidelines: mild (awareness of sign or symptom, but easily tolerated), moderate (discomfort enough to cause interference with usual activity) and severe (incapacitating or unable to work or perform usual activities).

Statistical Analysis

The primary variables of analysis for efficacy were mean IOP and the mean change in IOP from baseline. These IOP data were analyzed using both the intent-to-treat with last observation carried forward and per-protocol populations. The per-protocol population consisted of observed cases. Only patients who met the protocol entry criteria, had no major protocol violations, received study medication, and had at least one follow-up visit were included in the per-protocol analysis, and only data from visits within specified time windows were included. Decisions for per-protocol exclusions were made before unmasking of the treatment groups for analysis. Safety data were analyzed using the intent-to-treat population. For comparison of treatment efficacy, both noninferiority and a two-sided paired t test for superiority were performed. Noninferiority criteria were set by the US Food and Drug Administration. Criteria were tested by constructing a two-sided 95% confidence interval for the between-group difference between experimental drug and brimonidine in mean IOP. If the upper limit of 95% confidence interval at all time points did not exceed 1.5 mm Hg, brimonidine-Purite was considered at least as effective as brimonidine.

Nominal categorical data such as sex and race were analyzed by the Cochran-Mantel-Haenszel method and continuous variables such as age and blood pressure were analyzed using a two-way analysis of variance with factors of treatment group and investigator site. Adverse events were analyzed using the Pearson χ^2 test or Fisher exact test. Ordinal categorical variables such as comfort and safety data were analyzed using the stratum (investigator site) adjusted Kruskal-Wallis and Wilcoxon rank-sum test.

RESULTS

Subject Demographics

The demographics and clinical characteristics of patients taking brimonidine-Purite 0.15% three times daily, brimonidine-Purite 0.2% three times daily, and brimonidine 0.2% three times daily are summarized in Table 1. No significant between-group differences were noted in baseline demographics, which included mean patient age, gender, race, and iris color.

Efficacy

Criteria for the per-protocol analysis were met by 97.9% (1,123 of 1,147) of patients (brimonidine-Purite 0.15%, 97.6% [372 of 381 patients]; brimonidine-Purite 0.2%, 97.9% [375 of 383 patients]; brimonidine 0.2%, 98.2% [376 of 383 patients]) and 92% of all data points were included with a similar distribution across the treatments. Twenty-four patients did not meet the entry criteria as defined in the study protocol and were excluded from the efficacy analysis. Other key reasons for patient data exclusions from the per-protocol analysis included use of excluded medications during the study, inappropriate instillation of study medications, and visits occurring outside of visit windows. There was no significant difference in the IOP results between the intent-to-treat and per-protocol analyses, and the per-protocol results are presented. The conclusions drawn from either intent-to-treat or per-protocol populations were the same.

Overall IOP Efficacy

At baseline, mean IOP was similar across the three treatment groups at each time point. Baseline mean IOP at 10 AM was 23.6 mm Hg (with an approximate SD of 3.2 mm Hg). Baseline mean IOP at 8 AM was 24.9 mm Hg (with an approximate SD of 2.7 mm Hg) (Fig. 1 and 2). Over the next 12 months, the difference in mean IOP at 10 AM (morning peak) (Fig. 1) and 8 AM (morning trough) (Fig. 2) between brimonidine-Purite 0.15% and brimonidine 0.2% was less than or equal to 0.4 mm Hg.

The mean IOP for each group was within 1 mm Hg of

TABLE 1. *Demographics and clinical characteristics of patients on brimonidine-Purite 0.15%, brimonidine-Purite 0.2%, and brimonidine 0.2%*

	Brimonidine-Purite 0.15% (n = 381)		Brimonidine-Purite 0.2% (n = 383)		Brimonidine 0.2% (n = 383)		Total (n = 1147)		
Variable	No.	(%)	No.	(%)	No.	(%)	No.	(%)	P
Age (years)									0.460
Mean	63.4		63.8		62.7		63.3		
SD	12.8		12.1		12.6		12.5		
Min	22.4		25.4		25.2		22.4		
Max	88.8		90.4		93.4		93.4		
Median	64.7		65.8		64.2		64.7		
Sex									0.845
Male	169	44.4%	162	42.3%	167	43.6%	498	43.4%	
Female	212	55.6%	221	57.7%	236	56.4%	649	56.6%	
Race									0.377
Caucasian	303	79.5%	298	77.8%	305	79.6%	906	79.0%	
Black	48	12.6%	59	15.4%	47	12.3%	154	13.4%	
Asian	2	0.5%	1	0.3%	3	0.8%	6	0.5%	
Hispanic	28	7.3%	23	6.0%	26	6.8%	77	6.7%	
Other	0	0.0%	2	0.5%	2	0.5%	4	0.3%	
Iris color									0.468
Blue	113	29.7%	108	28.2%	111	29.0%	332	28.9%	
Brown	179	47.0%	196	51.2%	183	47.8%	558	48.6%	
Green	23	6.0%	18	4.7%	18	4.7%	59	5.1%	
Hazel	59	15.5%	58	15.1%	68	17.8%	185	16.1%	
Other	7	1.8%	3	0.8%	3	0.8%	13	1.1%	

the mean IOP in the other groups at all visits and all time points, showing comparable IOP-lowering capabilities.

Brimonidine-Purite 0.15% Versus Brimonidine 0.2%

There were no statistically significant differences in diurnal mean IOP measurements between brimonidine-Purite 0.15% and brimonidine 0.2%, except at the 5-PM time point at month 3 (P = 0.046) where the mean IOP difference was 0.5 mm Hg in favor of brimonidine 0.2%. There were no statistically significant differences in the mean changes from baseline in diurnal IOP measurements, except for the 10-AM time point at week 2 (P = 0.015), the 5-PM time point at month 3 (P = 0.010), and the 5-PM time point at month 6 (P = 0.004). The mean

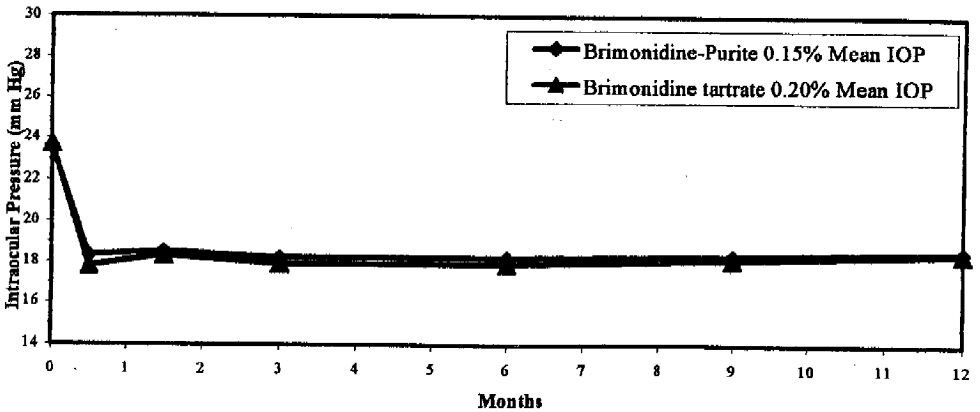

FIG. 1. Efficacy graph at 10 AM (peak) showing mean intraocular pressure of patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15% and brimonidine 0.2% (Alphagan). The difference in mean intraocular pressure between the treatment groups was less than or equal to 0.4 mm Hg at all time points. All standard errors were less than 0.180.

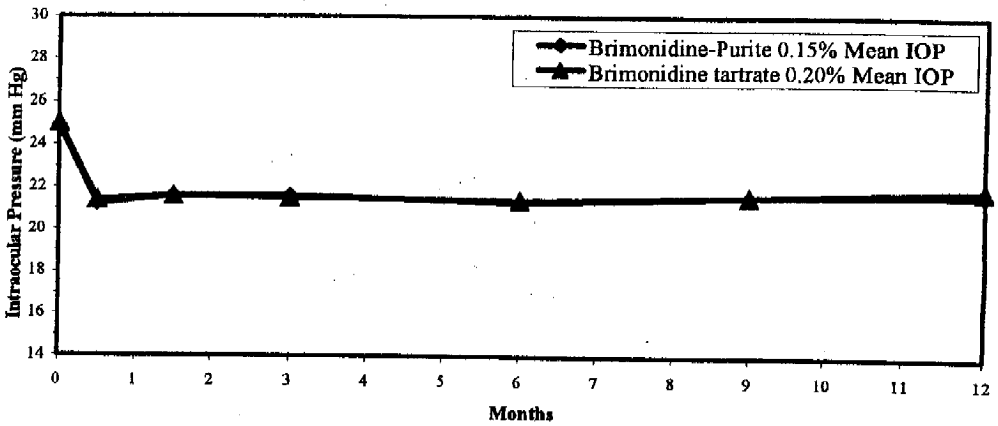

FIG. 2. Efficacy graph at 8 AM (trough) showing mean intraocular pressure of patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15% and brimonidine 0.2% (Alphagan). All standard errors were less than 0.211.

change from baseline IOP difference was 0.6, 0.7, and 0.9 mm Hg, respectively favoring brimonidine 0.2%. The noninferiority criteria were satisfied because 40/40 of the upper limits of 95% confidence intervals were less than or equal to 1.5 mm Hg, with 36/40 less than or equal to 1.0 mm Hg (mean IOP and mean change from baseline IOP), showing that brimonidine-Purite 0.15% was comparable in efficacy with brimonidine 0.2%.

Brimonidine-Purite 0.15% Versus Brimonidine-Purite 0.2%

There were no statistically significant differences observed in mean IOP or mean changes from baseline in diurnal IOP measurements between brimonidine-Purite 0.15% and brimonidine-Purite 0.2%, except at the 5-PM time point at month 3 ($P = 0.027$, mean IOP), the 10-AM time point at month 9 ($P = 0.009$, mean IOP), and the 10-AM time point at month 12 ($P = 0.011$, mean IOP). The mean IOP difference was 0.6, 0.8, and 0.8 mm Hg, respectively, favoring brimonidine-Purite 0.2%. The noninferiority criteria were satisfied because 40/40 of the upper limits of 95% confidence intervals were less than or equal to 1.5 mm Hg, with 35/40 less than or equal to 1.0 mm Hg (mean IOP and mean changes from baseline IOP), showing that brimonidine-Purite 0.15% was comparable in efficacy with brimonidine-Purite 0.2%.

Brimonidine-Purite 0.2% Versus Brimonidine 0.2%

In the comparison of brimonidine-Purite 0.2% and brimonidine 0.2%, there were no statistically significant differences observed in mean IOP or mean changes from baseline in diurnal IOP measurements except for the 10-AM time point at month 9 ($P = 0.045$, mean IOP), the 10-AM time point at month 12 ($P = 0.018$, mean IOP), and the 5-PM time point at month 12 ($P = 0.041$, mean IOP). The average difference in mean IOP and mean changes from baseline in IOP difference was –0.6, –0.8, and –0.7 mm Hg, respectively, favoring brimonidine-Purite 0.2%. The only measurement favoring brimonidine 0.2% was at the 10-AM time point at month 6 (mean change from baseline IOP difference of 0.7 mm Hg, $P = 0.019$). The noninferiority criteria were satisfied because 40/40 of the upper limits of the 95% confidence intervals were less than or equal to 1.5 mm Hg, with 37/40 less than or equal to 1.0 mm Hg (mean IOP and mean changes from baseline IOP), showing that brimonidine-Purite 0.2% was comparable in efficacy with brimonidine 0.2%.

Safety

The following results were analyzed as intent-to-treat, and all data points were considered. Throughout the study, patients were monitored for signs and symptoms of adverse events (Table 2). Investigators rated the majority of adverse events as mild or moderate in severity. The overall frequency of treatment-related adverse events reported was fewer in the brimonidine-Purite 0.15% than with brimonidine-Purite 0.2% or brimonidine 0.2%. There was a lower incidence rate of allergic conjunctivitis, conjunctival hyperemia, and oral dryness favoring brimonidine-Purite 0.15% compared

TABLE 2. *Summary of treatment-related adverse events of patients with glaucoma or ocular hypertension during twelve-month treatment with brimonidine-Purite 0.15%, brimonidine-Purite 0.2%, and brimonidine 0.2% (among group P-values). The second P-value is a summary of possible, probable, and definite treatment-related adverse events in pairwise comparison of patients with glaucoma or ocular hypertension during twelve-month treatment with brimonidine-Purite 0.15 and brimonidine 0.2%*

Adverse event	Brimonidine-Purite 0.15% (n = 381) No. (%)	Brimonidine-Purite 0.2% (n = 383) No. (%)	Brimonidine 0.2% (n = 383) No. (%)	Amongst group P	Brimonidine-Purite 0.15 vs. brimonidine 0.2% P
Allergic conjunctivitis	35 (9.2%)	56 (14.6%)	60 (15.7%)	0.018	0.007
Oral dryness	20 (5.3%)	36 (9.4%)	40 (10.4%)	0.024	0.008
Conjunctival hyperemia	69 (18.2%)	81 (21.1%)	98 (25.6%)	0.043	0.013
Eye discharge	5 (1.3%)	7 (1.8%)	15 (3.9%)	0.043	0.025

with the treatment groups. There was only a 0.8% incidence of somnolence with brimonidine-Purite 0.15% compared with 2.6% in brimonidine-Purite 0.2% and brimonidine 0.2%. Although this difference did not meet statistical significance, because it is a rare adverse event it could be clinically relevant.

Table 2 also shows a direct comparison of the adverse events between the subjects on brimonidine-Purite 0.15% and brimonidine 0.2%. This pairwise comparison showed a statistically significant difference favoring brimonidine-Purite 0.15% ($P < 0.001$) in overall incidence of adverse events. Statistically significant lower incidences of conjunctival hyperemia, allergic conjunctivitis, and oral dryness were shown in the brimonidine-Purite 0.15% group ($P \leq 0.013$).

There were no statistical differences in the visual acuity, cup/disc ratio, visual fields, heart rate, and systolic and diastolic blood pressure.

Quality of Life

There were no statistical differences in the investigators' response to the clinical success of the medications. However, there were significant differences in how patients rated their satisfaction with their study medication at the time of exit from the study. The level of satisfaction was greater for patients using brimonidine-Purite 0.15% than those using brimonidine 0.2% ($P = 0.005$) (Fig. 2). Although less statistically significant, the level of satisfaction was greater for patients using brimonidine-Purite 0.2% than those using brimonidine 0.2% ($P = 0.020$). There was no statistical difference between the level of satisfaction of patients using brimonidine-Purite 0.15% compared with those using brimonidine-Purite 0.2%.

Throughout the year, more than 90% of all the treatment groups rated their study medications as comfortable, very comfortable, or soothing (Fig. 3). However, there were significant differences in how patients rated the comfort of their study medication at the time of exit from the study. Significantly more patients reported that brimonidine-Purite 0.15% was more comfortable than brimonidine 0.2% ($P = 0.042$). Furthermore, patients reported that brimonidine-Purite 0.2% was more comfortable than brimonidine 0.2% ($P = 0.027$). There was no statistical significance between the level of comfort of patients using brimonidine-Purite 0.15% compared with those using brimonidine-Purite 0.2%.

Patient Discontinuations

The most frequent reasons cited for discontinuation (in descending order) were adverse events, lack of efficacy, administrative issues, and protocol violations. Lack of efficacy was cited as the reason for discontinuation in only 5.3% of these patients in all 3 groups.

There were no statistical differences among the groups regarding adverse events that led to discontinuation from the study ($P = 0.203$). A smaller percentage of patients, however, discontinued therapy in the brimonidine-Purite

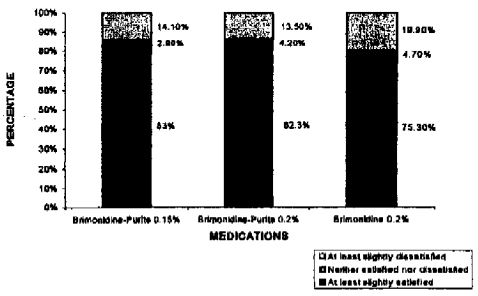

FIG. 3. Patient satisfaction evaluation summary for patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15%, brimonidine-Purite 0.2%, and brimonidine 0.2%. The among-group P of 0.010 is a comparison of the seven-category response distributions for the three treatment groups. Patients rated the level of satisfaction with their study medication at the time of exit from the study. The pairwise comparison of brimonidine-Purite 0.15% versus brimonidine 0.2% yielded a P of 0.005, favoring brimonidine-Purite 0.15%.

0.15% (21.8%) group than in the brimonidine-Purite-0.2% (24.8%) or brimonidine-0.2% (27.4%) groups. The most common adverse events leading to discontinuation were conjunctival hyperemia, allergic conjunctivitis, and eye pruritus. Indeed, 5.1% fewer patients in brimonidine-Purite 0.15% cited allergic conjunctivitis as reason for discontinuation compared to brimonidine 0.2% (P = 0.017).

DISCUSSION

In this pooled analysis of two identically designed, 12-month, randomized, multisite, double-masked, parallel-group studies, brimonidine-Purite 0.15% and 0.2% provided IOP lowering comparable with brimonidine 0.2% in patients with glaucoma or ocular hypertension. Overall, the new 0.15% concentration of the brimonidine-Purite formulation showed IOP efficacy clinically comparable with brimonidine 0.2% throughout this 1-year study.

The formulations were applied three times daily in this study. The mean IOP at trough (8-AM measurement, before morning drop) of all 3 groups was comparable to the mean IOP at trough in previous studies where brimonidine 0.2% was administered twice daily[2–4] In an earlier study, application of brimonidine 0.2% three times daily and twice daily provided comparable IOP lowering at morning trough.[24] This finding suggests that brimonidine-Purite 0.15% would have comparable efficacy on morning IOP whether applied twice daily or three times daily; this hypothesis is being tested in an ongoing clinical trial.

Brimonidine 0.2%, which has been marketed since 1996, has shown a favorable adverse event profile, except for allergic conjunctivitis. The incidence of allergic conjunctivitis with brimonidine 0.2% has been reported to be 12.7% with twice-daily dosing.[4] In this present study, the incidence of allergic conjunctivitis was 15.7% for patients taking brimonidine 0.2% three times daily The higher incidence of allergic conjunctivitis is likely related to the increased frequency of dosing. It is interesting that the incidence of allergic conjunctivitis with patients on brimonidine-Purite 0.15% three times daily, which contains 25% less active ingredient of brimonidine, was only 9.2%. This incidence rate is less than the 12.7% incidence rate previously reported. This finding strongly suggests that with a twice-daily dosing of brimonidine-Purite 0.15%, the incidence of allergic conjunctivitis may be even lower than the 9.2% incidence with three-times-daily dosage regimen. Furthermore, it appears that the decreased concentration of brimonidine is primarily responsible for the decreased incidence of allergic conjunctivitis. The relative percent difference in allergic conjunctivitis during this current 1-year study was at least 41% less with brimonidine-Purite 0.15% than with brimonidine-Purite 0.2% or brimonidine 0.2%. Brimonidine-Purite 0.15% also had a significantly lower incidence of oral dryness than brimonidine 0.2%. Although not statistically significant, the lower incidence of somnolence with brimonidine-Purite 0.15% could prove to be beneficial. These findings suggest that brimonidine-Purite 0.15% has a superior adverse-events profile compared with brimonidine 0.2%.

In addition to having a comparable IOP-lowering effect to brimonidine 0.2% solution and a superior adverse event profile, reformulated brimonidine-Purite 0.15% appears to be better tolerated than brimonidine 0.2%. Brimonidine-Purite 0.15% had a significantly higher rate of satisfaction (P = 0.005) and comfort (P = 0.042) than the original formulation (Figs. 2 and 3). At the patients' last visit, more than 80% were satisfied with the reformulated brimonidine-Purite 0.15%, and 84.6% (P = 0.042) found it to be comfortable. The higher comfort experienced by those in the brimonidine-Purite groups should lead to improved compliance with the antiglaucoma regimen. The potentially enhanced ocular bioavailability associated with the reformulation may also explain why brimonidine-Purite 0.15% shows efficacy comparable with brimonidine 0.2% with a lower concentration of active drug (Fig. 4).

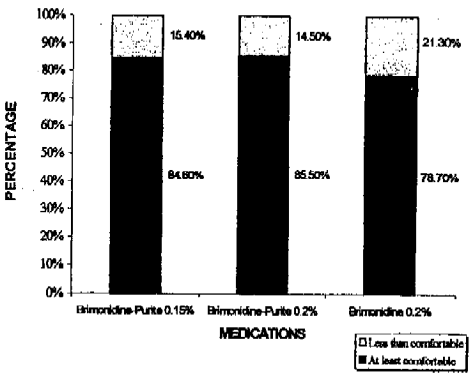

FIG. 4. Patient comfort evaluation summary for patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15%, brimonidine-Purite 0.2%, and brimonidine 0.2%. The among-group P of 0.049 is a comparison of the six-category response distributions for the three treatment groups. Patients rated the level of satisfaction with their study medication at the time of exit from the study. The pairwise comparison of brimonidine-Purite 0.15% versus brimonidine 0.2% yielded a P of 0.042, favoring brimonidine-Purite 0.15%.

CONCLUSIONS

Brimonidine-Purite at concentrations of 0.15% or 0.2% effectively lowers IOP in patients with glaucoma or ocular hypertension. Brimonidine-Purite 0.15% also shows comparable efficacy with brimonidine 0.2% with less than a 1-mm Hg difference between study drugs at all time points throughout this study. The brimonidine-Purite 0.15% concentration showed a more favorable safety and tolerability profile with a 41% relative percent reduction in ocular allergy when compared with brimonidine 0.2%. The brimonidine-Purite 0.15% formulation received superior satisfaction and comfort ratings. Based on these clinical findings, it can be concluded that brimonidine-Purite 0.15% is an effective, safe, and well-tolerated therapy for the long-term treatment of high IOP.

APPENDIX

Members of the Brimonidine-Purite Study Groups 1 and 2 investigators include (in alphabetical order) Mark Abelson, MD, Edward Andersen, MD, Amy Batoosingh BA, Richard S. Bennion, MD, E. Randy Craven, MD, Harvey DuBiner, MD, Richard Evans, MD, Carlos Felix, MS, William C. Flynn, MD, Daniel Foreman, MD, Gary N. Foulks, MD, Stephen Gee, MD, L. Jay Katz, MD, Alex Kent, MD, Jeff Lozier, MD, Jeffrey Morris, MD, Thomas Mundorf, MD, Charles S. Ostrov, MD, Matthew Parsons, MD, Jay Perlman, MD, PhD, Michael J. Price, MD, Arnold Prywes, MD, Edward R. Rashid, MD, Patrick Riedel, MD, Elenora Safyan, BS, Kenneth Sall, MD, John Samples, MD, Thomas Samuelson, MD, Howard I. Schenker, MD, Gail Schwartz, MD, PA, John D. Sheppard, MD, Dong H. Shin, MD, PhD, Steven Simmons, MD, Dara Stevenson, MD, William C. Stewart, MD, Richard T. Sturm, MD, Lloyd Suter, MD, Stuart A. Terry, MD, Christopher M. Tortora, MD, Thomas R. Walters, MD, Mark Weiss, MD, Sidney Weiss, MD, Robert D. Williams, MD, Lisa Wohl, MD, SC, Eugene Barry Wolchok, MD, and Brandon Wool, MD.

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DOCKET NO. 1758.1(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik et al	Group Art Unit: 1615
Serial No: 10/236,566	Examiner: Bennett, R.
Filed: September 6, 2002	
For: COMPOSITIONS CONTAINING ALPHA-2-AGONIST ADRENERGIC AGONIST COMPONENTS	

Commissioner of Patents
Washington, D.C. 20231

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING PATENT APPLICATION

Dear Sir:

The owner, Allergan Sales, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 and 156 and 173, as may be presently shortened by any terminal disclaimer, of any patent first issuing on co-pending United States Patent Application No. 09/904,018. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent issuing from the above- identified patent application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 to 156 and 173 of any patent issuing from United States Patent Application No. 09/904,018, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminal

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disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The undersigned is an attorney of record.

Date: 3/14/03

By: Carlos A. Fisher

Carlos A. Fisher
Reg. No. 36,510

ALLERGAN SALES, INC.

X Please charge the terminal disclaimer fee under 37 CFR 1.20(d) to Account No. 01-0885. A duplicate of this terminal disclaimer is enclosed.

Please direct all future correspondence to:

Carlos A. Fisher (T2-7H)
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ALLERGAN, INC.
2525 Dupont Drive
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Fax: 714/246-4249

DOCKET NO. 17361CON(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik et al	Group Art Unit: 1615
Serial No: 10/236,566	Examiner: Bennett, R.
Filed: September 6, 2002	
For: COMPOSITIONS CONTAINING ALPHA-2-AGONIST ADRENERGIC AGONIST COMPONENTS	

#9

Commissioner of Patents
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TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER BOTH AN ISSUED PATENT AND A PENDING PATENT APPLICATION

Dear Sir:

The owner, ALLERGAN SALES, LLC, successor by operation of law to Allergan Sales, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 and 156 and 173, as may be presently shortened by any terminal disclaimer, of 1) any patent issuing on co-pending United States Patent Application No. 09/904,018 and on 2) issued United States Patent 6,562,873. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it, any patent issuing from the above- identified patent application, and the above-identified patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 to 156 and 173 of either 1) any patent issuing from United States Patent Application No. 09/904,018, or 2) issued United States Patent 6,562,873 as presently shortened by any terminal disclaimer, in the event that one

or both of the latter: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminal disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The undersigned is an attorney of record.

Date: 5/19/03

By: _____
Carlos A. Fisher
Reg. No. 36,510

ALLERGAN SALES, LLC

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Please direct all future correspondence to:

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May-19-03 03:03pm From-ALLERGAN LEGAL DEPARTMENT +17142464249 T-987 P.04/06 F-267

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FROM: Carlos A. Fisher
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In re: Olejnik, et al.

Appln. No.: 10/236,566

Filed: September 6, 2002

Title: COMPOSITIONS CONTAINING ALPHA-2-AGONIST ADRENERGIC AGONIST COMPONENTS

Docket No. 17361CON(AP)

Date: May 19, 2003

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In re: Olejnik, et al.

Appln. No.: 10/236,566

Filed: September 6, 2002

Docket No. 17361CON(AP)

Date: May 19, 2003

Title: COMPOSITIONS CONTAINING ALPHA-2-AGONIST ADRENERGIC AGONIST COMPONENTS

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Interview Summary	Application No. 10/236,566	Applicant(s) OLEJNIK ET AL.	
	Examiner Rachel M. Bennett	Art Unit 1615	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Rachel M. Bennett*. (3)_____.

(2) *Carlos Fisher*. (4)_____.

Date of Interview: *May 19 & 21, 2003*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *on record*.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The attorney of record and examiner agreed to cancel claims 52 and 62. Claims 47 and 57 would be amended to "about" 21 deg C. Support for the amendment is found on page 30, line 22 of the specification*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Rachel M. Bennett
Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

mmary of Record of Interview Requireme

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) If appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Notice of Allowability	Application No.	Applicant(s)	
	10/236,566	OLEJNIK ET AL.	
	Examiner	Art Unit	
	Rachel M. Bennett	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Amendment B filed 3/24/03 and Terminal Disclaimer filed 5/19/03*.
2. ☒ The allowed claim(s) is/are *47-51,53-61 and 63-70*.
3. ☒ The drawings filed on *9/6/02* are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

8. ☐ CORRECTED DRAWINGS must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet.

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Informal Patent Application (PTO-152)
3☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
4☒ Interview Summary (PTO-413), Paper No. *10* .
5☐ Information Disclosure Statements (PTO-1449), Paper No. ____.
6☒ Examiner's Amendment/Comment
7☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8☐ Examiner's Statement of Reasons for Allowance
9☐ Other .

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

U.S. Patent and Trademark Office
PTO-37 (Rev. 04-03) **Notice of Allowability** Part of Paper No. 11 .

DETAILED ACTION

The examiner acknowledges receipt of Amendment B filed 3/24/03.

Terminal Disclaimer

1. The terminal disclaimer filed on 5/19/03 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent Application 09/904,018 or US Patent 6,562,873 has been reviewed and is accepted. The terminal disclaimer has been recorded.

2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Carlos Fisher on May 19, 2003.

The application has been amended as follows:

Please cancel claims 52 and 62.

Please amend claim 47, line 4, insert "about" before "21°C".

Please amend claim 57, line 6, insert "about" before "21°C".

Allowable Subject Matter

3. Claims 47-51, 53-61, 63-70 are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel M. Bennett whose telephone number is (703) 308-8779. The examiner can normally be reached on Monday through Friday, 8:00 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (703) 308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

R. Bennett
May 23, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

33197 7590 06/03/2003

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618

EXAMINER	
BENNETT, RACHEL M	
ART UNIT	CLASS-SUBCLASS
1615	424-427000

DATE MAILED: 06/03/2003

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/236,566	09/06/2002	Orest Olejnik	D-2892CON	3779

TITLE OF INVENTION: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1300	$300	$1600	09/03/2003

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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Alexandria, Virginia 22313-1450
Fax (703)746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

33197 7590 06/03/2003

STOUT, UXA, BUYAN & MULLINS LLP
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IRVINE, CA 92618

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/236,566	09/06/2002	Orest Olejnik	D-2892CON	3779

TITLE OF INVENTION: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1300	$300	$1600	09/03/2003

EXAMINER	ART UNIT	CLASS-SUBCLASS
BENNETT, RACHEL M	1615	424-427000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) ☐ individual ☐ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

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☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Commissioner is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

Commissioner for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE; The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/236,566	09/06/2002	Orest Olejnik	D-2892CON	3779

33197 7590 06/03/2003

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618

EXAMINER	
BENNETT, RACHEL M	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 06/03/2003

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The patent term adjustment to date is 0 days. If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the term adjustment will be 0 days.

If a continued prosecution application (CPA) was filed in the above-identified application, the filing date that determines patent term adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system. (http://pair.uspto.gov)

Any questions regarding the patent term extension or adjustment determination should be directed to the Office of Patent Legal Administration at (703)305-1383.

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/236,566	09/06/2002	Orest Olejnik	D-2892CON	3779

33197 7590 06/03/2003

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618
UNITED STATES

EXAMINER	
BENNETT, RACHEL M	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 06/03/2003

Notice of Fee Increase on January 1, 2003

If a reply to a "Notice of Allowance and Fee(s) Due" is filed in the Office on or after January 1, 2003, then the amount due will be higher than that set forth in the "Notice of Allowance and Fee(s) Due" since there will be an increase in fees effective on January 1, 2003. See Revision of Patent and Trademark Fees for Fiscal Year 2003: Final Rule, 67 Fed. Reg. 70847, 70849 (November 27, 2002).

The current fee schedule is accessible from: http://www.uspto.gov/main/howtofees.htm.

If the issue fee paid is the amount shown on the "Notice of Allowance and Fee(s) Due," but not the correct amount in view of the fee increase, a "Notice to Pay Balance of Issue Fee" will be mailed to applicant. In order to avoid processing delays associated with mailing of a "Notice to Pay Balance of Issue Fee," if the response to the Notice of Allowance and Fee(s) due form is to be filed on or after January 1, 2003 (or mailed with a certificate of mailing on or after January 1, 2003), the issue fee paid should be the fee that is required at the time the fee is paid. If the issue fee was previously paid, and the response to the "Notice of Allowance and Fee(s) Due" includes a request to apply a previously-paid issue fee to the issue fee now due, then the difference between the issue fee amount at the time the response is filed and the previously paid issue fee should be paid. See Manual of Patent Examining Procedure, Section 1308.01 (Eighth Edition, August 2001).

Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004.

JUN 11 2003 JC40 PATENT & TRADEMARK OFFICE

11:17AM FROM-Frank 8494501764 T-168 P.002/003 F-550

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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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23197 7590 06/05/2003

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JANET McGHEE (Depositor's name)
Janet McGhee (Signature)
JUNE 11, 2003 (Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/236,566	09/06/2002	Oren Olejnik	D-2001CON	3779

TITLE OF INVENTION: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1500	$300	$1800	09/09/2003

EXAMINER	ART UNIT	CLASS-SUBCLASS
BENNETT, RACHEL M	1615	424-427000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☒ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Stout, Uxa, Buyan & Mullins, LLP
2 Frank J. Uxa
3 Carlos A. Fisher

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)
PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.
(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)
ALLERGAN SALES, INC. IRVINE, CA

Please check the appropriate assignee category or categories (will not be printed on the patent) ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:
☒ Issue Fee
☒ Publication Fee
☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):
☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Commissioner is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 08-01-0885 (enclosed an extra copy of this form).

Commissioner for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

OK to Enter

(Authorized Signature) (Date) 6/11/03

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

06/12/2003 AWONDAF2 00000028 010885 10236566
01 FC:1501 1300.00 CH
02 FC:1504 300.00 CH
03 FC:8001 30.00 CH

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

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Received from <8494501764> at 6/11/03 2:38:15 PM [Eastern Daylight Time]

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PTO/SB/122 (10-01)
Approved for use through 10/31/2002. OMB 0651-0035
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CHANGE OF CORRESPONDENCE ADDRESS
Application

Address to:
Commissioner for Patents
Washington, D.C. 20231

Application Number	10/236,566 → 10/236566
Filing Date	September 6, 2002
First Named Inventor	Olejnik
Art Unit	1615
Examiner Name	Bennett, R.M.
Attorney Docket No.	D-2992 CON

Please change the Correspondence Address for the above-identified application to:

☐ Customer Number _____ (Customer Number) → _____ (Customer Number Bar Code)

OR

☒ Firm or Individual name	Carlos A. Fisher				
Address	Allergan, Inc. 2525 Dupont Drive				
City	Irvine	State	CA	Zip	92627
Country	US				
Telephone	714-246-4920	Fax	714-246-4249		

This form cannot be used to change the data associated with a Customer Number. To change the data associated with an existing Customer Number use "Request for Customer Number Data Change" (PTO/SB/124).

I am the:

☐ Applicant/Inventor.

☐ Assignee of record of the entire interest.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ Attorney or Agent of record.

☐ Registered practitioner named in the application transmittal letter in an application without an executed oath or declaration. See 37 CFR 1.33(a)(1). Registration Number _____

Typed or Printed Name: Frank J. Uxa

Signature: Frank J. Uxa

Date: 6/11/03

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

1/1

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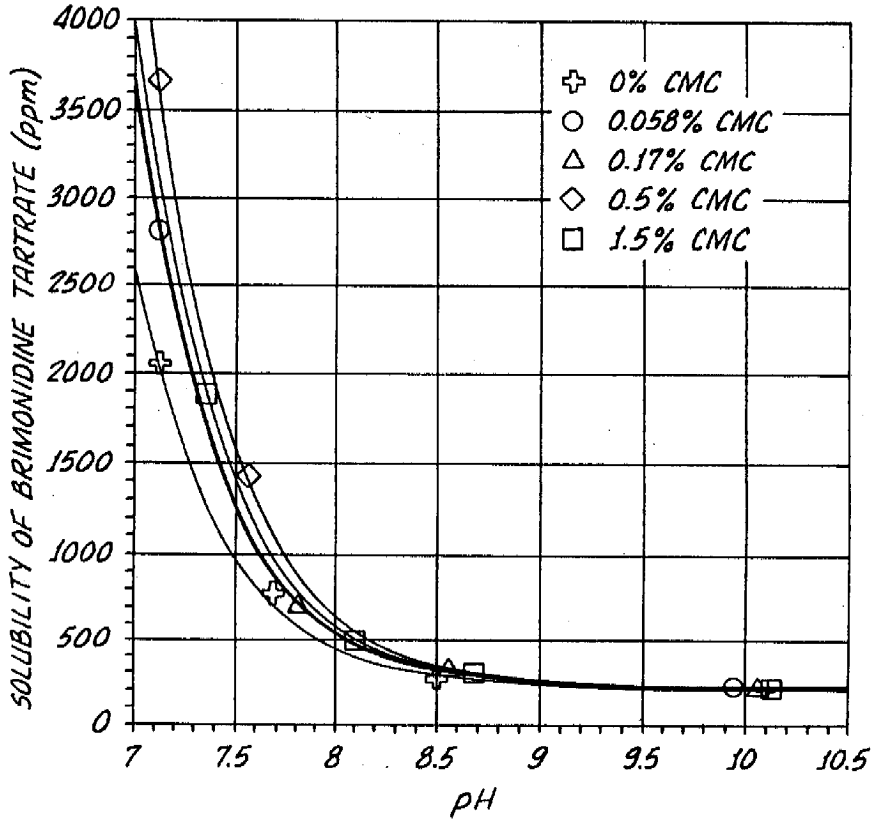

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: D-2892Conl.

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	20	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	20 minus 20=	*0
INDEPENDENT CLAIMS	2 minus 3 =	*0
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	740.00
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL		OR	TOTAL	740.00

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDI-TIONAL FEE		RATE	ADDI-TIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDI-TIONAL FEE		RATE	ADDI-TIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDI-TIONAL FEE		RATE	ADDI-TIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev. 8/01) *U.S. Government Printing Office: 2001 — 484-484/59268 Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

CLAIMS ONLY

SERIAL NO.	FILING DATE
APPLICANT(S)	

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
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50						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
53						
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56						
57	1					
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97						
98						
99						
100						
TOTAL IND.	2					
TOTAL DEP.	18					
TOTAL CLAIMS	20					

* MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

FORM PTO-2022 (1-98)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

*U.S. Government Printing Office: 1998 - 433-214/70303

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SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934

For The Fiscal Year Ended December 31, 2004

Commission File No. 1-10269

Allergan, Inc.

(Exact name of Registrant as Specified in its Charter)

Delaware	**95-1622442**
(State of Incorporation)	*(I.R.S. Employer Identification No.)*
2525 Dupont Drive	**92612**
Irvine, California	*(Zip Code)*
(Address of principal executive offices)	

(714) 246-4500
(Registrant's telephone number)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which each class registered
Common Stock, $0.01 par value	New York Stock Exchange
Preferred Share Purchase Rights	

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months, and (2) has been subject to such filing requirements for the past 90 days. Yes ☑ No ☐ .

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☑

Indicate by check mark whether the registrant is an accelerated filer (as defined in Exchange Act Rule 12b-2). Yes ☑ No ☐ .

The aggregate market value of the registrant's common equity held by non-affiliates was approximately $11,819 million on June 25, 2004, based upon the closing price on the New York Stock Exchange on such date.

Common Stock outstanding as of February 25, 2005 — 134,254,772 shares (including 2,649,633 shares held in treasury).

DOCUMENTS INCORPORATED BY REFERENCE

Part III incorporates certain information by reference from the registrant's proxy statement for the annual meeting of stockholders to be held on April 26, 2005, which proxy statement will be filed no later than 120 days after the close of the registrant's fiscal year ended December 31, 2004.

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PART I

Item 1. *Business*

General Development of Our Business

Allergan, Inc. is a technology-driven, global health care company that develops and commercializes specialty pharmaceutical products for the ophthalmic, neurological, dermatological and other specialty markets. We are a pioneer in specialty pharmaceutical research, targeting products and technologies related to specific disease areas such as glaucoma, retinal disease, dry eye, psoriasis, acne and movement disorders. Additionally, we develop and market aesthetic-related pharmaceuticals and over-the-counter products. Within these areas, we are an innovative leader in therapeutic and other prescription products, and to a limited degree, over-the-counter products that are sold in more than 100 countries around the world. We are also focusing research and development efforts on new therapeutic areas, including gastroenterology, neuropathic pain and genitourinary diseases.

We were originally incorporated in California in 1948 and became known as Allergan Corporation in 1950. In 1977, we reincorporated in Delaware. In 1980, we were acquired by SmithKline Beecham plc (then known as SmithKline Corporation). From 1980 through 1989, we operated as a wholly-owned subsidiary of SmithKline and in 1989 we again became a stand-alone public company through a spin-off distribution by SmithKline.

Our Internet website address is www.allergan.com. We make our periodic and current reports, together with amendments to these reports, available on our Internet website, free of charge, as soon as reasonably practicable after such material is electronically filed with, or furnished to, the Securities and Exchange Commission. The information on our Internet website is not incorporated by reference in this Annual Report on Form 10-K.

In June 2002, we completed the spin-off of our optical medical device business to our stockholders. The optical medical device business consisted of two businesses: our ophthalmic surgical products business and our contact lens care products business. The spin-off was effected by contributing our optical medical device business to a newly formed subsidiary, Advanced Medical Optics, Inc., or AMO, and issuing a dividend of AMO's common stock to our stockholders. Our consolidated financial statements and related notes reflect the financial position, results of operations and cash flows of the optical medical device business as a discontinued operation.

In October 2004, our board of directors approved certain restructuring activities related to the scheduled termination of our manufacturing and supply agreement with AMO. Under the manufacturing and supply agreement, which was entered into in connection with the AMO spin-off, we agreed to manufacture certain products for AMO for a period of up to three years ending in June 2005. As part of the termination of the manufacturing and supply agreement, we will eliminate certain manufacturing positions at our Westport, Ireland; Waco, Texas; and Guarulhos, Brazil manufacturing facilities. We anticipate that the pre-tax restructuring charges to be incurred in connection with the termination of the manufacturing and supply agreement will total between $24 million and $28 million and that there will be a reduction in our workforce of approximately 350 individuals.

In January 2005, our board of directors approved the initiation and implementation of a restructuring of certain activities related to our European operations. The restructuring seeks to optimize operations, improve resource allocation and create a scalable, lower cost and more efficient operating model for our European research and development and commercial activities. Specifically, the restructuring anticipates moving key European research and development and select commercial functions from our Mougins, France and other European locations to our Irvine, California, High Wycombe, U.K. and Dublin, Ireland facilities and streamlining our European commercial back office functions. Under applicable law, the proposed restructuring requires consultations and, in certain cases, negotiations with European and national works councils, other management/ labor organizations and local authorities. The restructuring steps to be implemented and their ultimate cost will depend in part on the outcome of such consultations and negotiations. We anticipate

incurring restructuring charges and charges relating to severance, relocation and one-time termination benefits, payments to public employment and training programs, implementation, transition, capital and other asset-related expenses, duplicate operating expenses and contract termination costs in connection with the restructuring. We currently estimate that the pre-tax charges and capital expenditures resulting from the restructuring will be between $50 million and $60 million. We also estimate that the restructuring will yield annual operating cost reductions of between $6 million and $9 million.

Our Business

The following table sets forth, for the periods indicated, net sales from continuing operations for each of our specialty pharmaceutical product lines, earnings (loss) from continuing operations, domestic and international sales as a percentage of total net sales and domestic and international long-lived assets:

	Year Ended December 31,		
	2004	2003	2002
		(In millions)	
Net Sales by Product Line			
Eye Care Pharmaceuticals	$1,137.1	$ 999.5	$ 827.3
Botox ®/ Neuromodulator	705.1	563.9	439.7
Skin Care Products	103.4	109.3	90.2
Other(1)	100.0	82.7	27.8
Total	$2,045.6	$1,755.4	$1,385.0
Earnings (loss) from continuing operations	$ 377.1	$ (52.5)	$ 64.0
Sales			
Domestic	69.1%	70.4%	70.6%
International	30.9%	29.6%	29.4%
Long-Lived Assets			
Domestic	$ 593.9	$ 573.8	$ 381.2
International	$ 287.1	$ 252.9	$ 225.2

(1) Other sales primarily consist of sales to AMO pursuant to a manufacturing and supply agreement entered into as part of the AMO spin-off that is scheduled to terminate in June 2005.

See Note 15, "Business Segment Information," in the notes to the consolidated financial statements listed under Item 15 (a) of Part IV of this report for further information concerning our foreign and domestic operations.

Eye Care Pharmaceutical Product Line

We develop, manufacture and market a broad range of prescription and non-prescription products designed to treat diseases and disorders of the eye, including glaucoma, dry eye, inflammation, infection and allergy.

Glaucoma. The largest segment of the market for ophthalmic prescription drugs is for the treatment of glaucoma, a sight-threatening disease typically characterized by elevated intraocular pressure leading to optic nerve damage. Glaucoma is currently the world's second leading cause of blindness, and we estimate that over 60 million people worldwide have glaucoma. According to IMS Health Inc., an independent research firm, our products for the treatment of glaucoma, including *Alphagan* ®, *Alphagan* ® *P* and *Lumigan* ®, captured approximately 17% of the worldwide glaucoma market for the first nine months of 2004.

Our largest selling eye care pharmaceutical products are the ophthalmic solutions *Alphagan* ® (brimonidine tartrate ophthalmic solution) 0.2% and *Alphagan* ® *P* (brimonidine tartrate ophthalmic solution)

0.15%, preserved with *Purite* ®. *Alphagan* ® and *Alphagan* ® *P* lower intraocular pressure by reducing aqueous humor production and increasing uveoscleral outflow. *Alphagan* ® *P* is an improved reformulation of *Alphagan* ® containing brimonidine, *Alphagan* ®'s active ingredient, preserved with *Purite* ®. We currently market *Alphagan* ® and *Alphagan* ® *P* in over 70 countries worldwide.

Alphagan ® and *Alphagan* ® *P* combined were the third best selling glaucoma products in the world for the first nine months of 2004, according to IMS Health Inc. Combined sales of *Alphagan* ® and *Alphagan* ® *P* represented approximately 13% of our total consolidated sales in 2004, 16% of our total consolidated sales in 2003 and 18% of our total consolidated sales in 2002. In July 2002, based on the acceptance of *Alphagan* ® *P*, we discontinued the U.S. distribution of *Alphagan* ®. In May 2004, we entered into an exclusive licensing agreement with Kyorin Pharmaceutical Co., Ltd., under which Kyorin agreed to be responsible for the development and commercialization of *Alphagan* ® and *Alphagan* ® *P* in Japan's ophthalmic specialty area. Kyorin agreed to incur associated costs and provided us with an up-front payment. Kyorin also agreed to make development and commercialization milestone payments to us, as well as royalty-based payments on product sales. We agreed to work collaboratively with Kyorin on overall product strategy and management. Kyorin subsequently sub-licensed its rights under the agreement to Senju Pharmaceutical Co., Ltd. The marketing exclusivity period for *Alphagan* ® *P* expired in the U.S. in September 2004, although we have a number of patents covering the *Alphagan* ® *P* technology that extend to 2021 in the U.S. and 2009 in Europe, with corresponding patents pending in Europe. In May 2003, the first generic form of *Alphagan* ® was approved by the U.S. Food and Drug Administration, or FDA. Additionally, a generic form of *Alphagan* ® is sold in a limited number of other countries, including Canada, Mexico, India, Brazil, Colombia and Argentina. See Item 3 of Part I of this report, "Legal Proceedings" and Note 13, "Commitments and Contingencies," in the notes to the consolidated financial statements listed under Item 15(a) of Part IV of this report for further information regarding litigation involving *Alphagan* ®. Falcon Pharmaceuticals, Ltd., an affiliate of Alcon Laboratories, Inc., is attempting to obtain FDA approval for and to launch a brimonidine product to compete with our *Alphagan* ® *P* product. In May 2004, we filed a New Drug Application with the FDA for a new formulation of *Alphagan* ® *P*. This New Drug Application remains pending.

Lumigan ® (bimatoprost ophthalmic solution) 0.03% is a topical treatment indicated for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who are either intolerant or insufficiently responsive when treated with other intraocular pressure-lowering medications. Sales of *Lumigan* ® represented approximately 11% of our total consolidated sales in 2004, 10% of our total consolidated sales in 2003 and 9% of our total consolidated sales in 2002. In March 2002, the European Commission approved *Lumigan* ® through its centralized procedure. In January 2004, the European Union's Committee for Proprietary Medicinal Products approved *Lumigan* ® as a first-line therapy for the reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension. We currently sell *Lumigan* ® in over 40 countries worldwide. In May 2004, we entered into an exclusive licensing agreement with Senju Pharmaceutical Co., Ltd., under which Senju is responsible for the development and commercialization of *Lumigan* ® in Japan's ophthalmic specialty area. Senju will incur associated costs and provided us with an up-front payment. Senju will also make development and commercialization milestone payments to us, as well as royalty-based payments on product sales. We will work collaboratively with Senju on overall product strategy and management.

In September 2001, we filed a New Drug Application with the FDA for a brimonidine and timolol combination designed to treat glaucoma. This New Drug Application remains pending. During the fourth quarter of 2003, we received approval from Health Canada for our brimonidine and timolol combination, which is marketed as *Combigan* ™. In December 2004, we received our first European approval of *Combigan* ™ in Switzerland. In November 2003, we filed a New Drug Application with the FDA for a *Lumigan* ® and timolol combination designed to treat glaucoma or ocular hypertension. In August 2004, we announced that the FDA issued an approvable letter regarding the *Lumigan* ® and timolol combination, setting out the conditions, including additional clinical investigation, that we must meet in order to obtain final FDA approval.

Ocular Surface Disease. In December 2002, the FDA approved *Restasis*® (cyclosporine ophthalmic emulsion) 0.05%, the first and currently the only prescription therapy for the treatment of chronic dry eye

disease. We launched *Restasis*® in the United States in April 2003. Dry eye disease is a painful and irritating condition involving abnormalities and deficiencies in the tear film initiated by a variety of causes. The incidence of dry eye disease increases markedly with age, after menopause in women and in people with systemic diseases such as Sjogren's syndrome and rheumatoid arthritis. Until the approval of *Restasis*® , physicians used lubricating tears as a temporary measure to provide palliative relief of the debilitating symptoms of dry eye disease. In June 2001, we entered into a licensing, development and marketing agreement with Inspire Pharmaceuticals, Inc. under which we obtained an exclusive license to develop and commercialize Inspire's INS365 Ophthalmic in exchange for royalty payments to Inspire on sales of both *Restasis*® and, ultimately, INS365. INS365 completed Phase III clinical trials investigating its ability to relieve the signs and symptoms of dry eye disease by rehydrating conjunctival mucosa and increasing non-lacrimal tear component production. In December 2003, the FDA issued an approvable letter for INS365 and also requested additional clinical data. In February 2005, Inspire announced that INS365 failed to demonstrate statistically significant improvement as compared to a placebo for the primary endpoint of the incidence of corneal clearing. Inspire also announced that INS365 achieved improvement compared to a placebo for a number of secondary endpoints, and that Inspire intends to file a New Drug Application amendment with the FDA by the end of the second quarter of 2005.

Ophthalmic Inflammation. Our leading ophthalmic anti-inflammatory product is *Acular* ® (ketorolac ophthalmic solution) 0.5%. *Acular* ® is a registered trademark of and is licensed from its developer, Syntex (U.S.A.) Inc., a business unit of Hoffmann-LaRoche Inc. *Acular* ® is indicated for the temporary relief of itch associated with seasonal allergic conjunctivitis, the inflammation of the mucus membrane that lines the inner surface of the eyelids, and for the treatment of post-operative inflammation in patients who have undergone cataract extraction. *Acular PF* ® was the first, and currently remains the only, unit-dose, preservative-free topical non-steroidal anti-inflammatory drug in the United States. *Acular PF* ® is indicated for the reduction of ocular pain and photophobia following incisional refractive surgery. *Acular* ® is the number one prescribed non-steroidal anti-inflammatory in the United States. See Item 3 of Part I of this report, "Legal Proceedings" and Note 13, "Commitments and Contingencies," in the notes to the consolidated financial statements listed under Item 15(a) of Part IV of this report for information regarding our successful patent infringement lawsuit against Apotex, Inc., et al. confirming the validity and enforceability of our intellectual property covering *Acular* ®. Apotex, Inc. subsequently appealed that judgment and we are currently awaiting the United States Court of Appeals for the Federal Circuit's ruling on the appeal.

In June 2003, we received FDA approval of *Acular LS*® , a reformulated ketorolac 0.4% concentration, for the reduction of ocular pain, burning and stinging following corneal refractive surgery. We launched *Acular LS* ® in the United States in August 2003.

Our product *Pred Forte*® remains a leading topical steroid worldwide based on 2004 sales. *Pred Forte*® has no patent protection or marketing exclusivity and faces generic competition.

Ophthalmic Infection. A leading product in the ophthalmic anti-infective market is our *Ocuflox* ® / *Oflox* ® / *Exocin* ® ophthalmic solution. *Ocuflox* ® has no patent protection or marketing exclusivity and faces generic competition.

In March 2003, we received FDA approval of *Zymar*® (gatifloxacin ophthalmic solution) 0.3%. *Zymar*® is the first fourth-generation fluoroquinilone to enter the market for the treatment of bacterial conjunctivitis. Laboratory studies have shown that *Zymar*® kills the most common bacteria that cause eye infections as well as specific resistant bacteria. We launched *Zymar*® in the United States in April 2003. According to Verispan, an independent research firm, *Zymar*® was the number one ocular anti-infective prescribed by ophthalmologists in the United States in 2004.

Allergy. The allergy market is, by its nature, a seasonal market, peaking during the spring months. We market *Alocril*® ophthalmic solution for the treatment of itch associated with allergic conjunctivitis. Additionally, in October 2003, we received FDA approval of *Elestat* ™ (epinastine ophthalmic solution) 0.05%, for the prevention of itching associated with allergic conjunctivitis. In December 2003, we announced the execution of an agreement with Inspire Pharmaceuticals for the co-promotion of *Elestat* ™ in the United States within the ophthalmic specialty area and to allergists. Under the terms of the agreement, Inspire

provided us with an up-front payment and we make payments to Inspire based on *Elestat* ™ net sales. In addition, the agreement reduced our existing royalty payment to Inspire for *Restasis* ®. Inspire has primary responsibility for selling and marketing activities in the United States related to *Elestat* ™. We have retained all international marketing and selling rights. We launched *Elestat* ™ in Europe under the brand names *Relestat* ® and *Purivist* ® during 2004, and Inspire launched *Elestat* ™ in the United States during 2004.

Neuromodulator

Our neuromodulator product, *Botox* ® (Botulinum Toxin Type A), is used for a wide variety of treatments which continue to expand. *Botox* ® is accepted in many global regions as the standard therapy for indications ranging from therapeutic neuromuscular disorders and related pain to cosmetic facial aesthetics. There are currently in excess of 100 therapeutic and cosmetic uses for *Botox* ® reported in medical literature. The versatility of *Botox* ® is based on its localized treatment effect and approximately 16 years of safety experience in large patient groups. Marketed as *Botox* ®, *Botox* ® Cosmetic, *Vistabel* ® or *Vistabex* ®, depending on the indication and country of approval, the product is currently approved in over 70 countries for a broad range of indications. Sales of *Botox* ® represented approximately 34%, 32% and 32% of our total consolidated sales in 2004, 2003 and 2002, respectively.

Botox ®. *Botox*® is used therapeutically for the treatment of certain neuromuscular disorders which are characterized by involuntary muscle contractions or spasms. The approved therapeutic indications for *Botox* ® in the United States are as follows:

- blepharospasm, the uncontrollable contraction of the eyelid muscles which can force the eye closed and result in functional blindness;
- strabismus, or misalignment of the eyes, in people 12 years of age and over;
- cervical dystonia, or sustained contractions or spasms of muscles in the shoulders or neck in adults, along with the associated pain; and
- severe primary axillary hyperhidrosis (underarm sweating) that is inadequately managed with topical agents.

In many countries outside of the United States and Japan, *Botox* ® is also approved for treating blepharospasm, strabismus, cervical dystonia, hemifacial spasm, pediatric cerebral palsy, hyperhidrosis and post-stroke focal spasticity. We are currently pursuing new indication approvals for *Botox* ® in the United States, Japan and Europe, including headache, post-stroke focal spasticity and overactive bladder.

Botox ® *Cosmetic.* The FDA approved *Botox* ® in April 2002 for the temporary improvement in the appearance of moderate to severe glabellar lines in adult men and women age 65 or younger. Referred to as *Botox* ®, *Botox* ® Cosmetic, *Vistabel* ® or *Vistabex* ®, depending on the country of approval, this product is designed to relax wrinkle-causing muscles to smooth the deep, persistent, glabellar lines between the brow that often develop during the aging process. Health Canada approved *Botox* ® Cosmetic for similar use in Canada in April 2001. In 2004, we continued our previously launched direct-to-consumer marketing campaigns in Canada and the United States. These campaigns included television commercials and print advertising aimed at consumers and aesthetic specialty physicians. Currently, over 30 countries have approved the glabellar line indication for *Botox* ®, *Botox* ® Cosmetic, *Vistabel* ® or *Vistabex* ®, including Australia, Brazil, Canada, Denmark, France, Israel, Italy, Mexico, Norway, Poland, Portugal, Spain, Sweden, and Switzerland. In January 2005, we received a positive opinion from the European Union by way of the Mutual Recognition Process for *Vistabel* ®. The positive opinion was received in all twelve concerned member states in which we filed, including, among others, Austria, Hungary, Greece, Belgium and Finland. We now sponsor training of aesthetic specialty physicians in approved countries to further expand the base of qualified physicians using *Botox* ® , *Botox* ® Cosmetic, *Vistabel* ® or *Vistabex* ®.

Skin Care Product Line

Our skin care product line focuses on the high growth, high margin segments of the acne and psoriasis markets, particularly in the United States and Canada.

Tazarotene Products. We market *Tazorac* ® gel in the United States for the treatment of plaque psoriasis, a chronic skin disease characterized by dry red patches, and acne. We also market the cream formulation of *Tazorac* ® in the United States for the treatment of psoriasis and the topical treatment of acne. Under a co-promotion agreement for *Tazorac* ® in the United States, PediaMed Pharmaceuticals, Inc. markets *Tazorac* ® to the pediatric medical community and Proctor & Gamble markets *Tazorac* ® to general practitioners. We market *Tazorac* ® to dermatologists with our in-house sales force. We have also engaged Pierre Fabre Dermatologie as our promotion partner for *Zorac* ® in certain parts of Europe, the Middle East and Africa.

In October 2002, we received FDA approval of *Avage*® . *Avage* ® is a tazarotene cream indicated for the treatment of facial fine wrinkling, mottled hypo- and hyperpigmentation (blotchy skin discoloration) and benign facial lentigines (flat patches of skin discoloration) in patients using a comprehensive skin care and sunlight avoidance program. We launched *Avage* ® in the United States in January 2003.

In November 2003, we filed a New Drug Application with the FDA for oral tazarotene for the treatment of moderate to very severe psoriasis. In July 2004, the FDA Joint Dermatologic & Opthalmic Drugs and Drug Safety & Risk Management Advisory Committee recommended against approval of this New Drug Application, and in September 2004, the FDA issued a non-approvable letter. The FDA listed three non-approvability issues for oral tazarotene for the treatment of moderate to very severe psoriasis: (1) the development of an acceptable risk management program; (2) completion of a non-inferiority study in severe psoriasis; and (3) satisfaction of an FDA deficiency letter regarding the manufacture of the oral tazarotene capsules. We intend to continue working with the FDA toward our goal of bringing oral tazarotene to patients suffering from psoriasis.

In May 2004, we transferred certain rights to our pre-clinical programs and broad research portfolio in retinoid and rexinoid nuclear receptor compounds to Concurrent Pharmaceuticals, Inc., a privately held biopharmaceutical company. The clinical assets and compounds subject to the transaction included near-clinical compounds and were primarily derived from our retinoid program. The transaction was designed to provide Concurrent with a portfolio of development compounds and near-clinical candidates that would comprise a discovery engine with the potential to create a pipeline of product leads and follow-on programs. Under the terms of the transaction, we received equity in Concurrent, the right to designate one person to serve on Concurrent's board of directors, as well as the right to receive future milestone and royalty payments. As part of the transaction, our retinoid receptor research team joined Concurrent.

In January 2005, we launched *Prevage* ™ antioxidant cream, the first and only clinically tested antioxidant that not only reduces the appearance of fine lines and wrinkles, but also provides protection against environmental factors including sun damage, air pollution and cigarette smoke. Representing the next generation of antioxidants, *Prevage* ™ is a novel cosmeceutical containing 1% idebenone — a revolutionary, potent and effective new antioxidant. *Prevage* ™ is marketed to physicians.

Azelex® . *Azelex* ® cream is approved by the FDA for the topical treatment of mild to moderate inflammatory acne vulgaris. We market *Azelex* ® cream primarily in the United States.

M.D. Forte ®. We also develop and market glycolic acid-based skin care products. Our *M.D. Forte*® line of alpha hydroxy acid products are marketed to physicians.

Finacea ®. In 2003 we entered into a collaboration with Intendis, Inc. (formerly known as Berlex, Inc.) to jointly promote Intendis' topical rosacea treatment, *Finacea* ® (azelaic acid gel 15%). *Finacea* ® is the first new therapeutic class option to be approved by the FDA for the treatment of rosacea in more than a decade and has rapidly gained a leading position in the market.

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Employee Relations

At December 31, 2004, we employed approximately 5,030 persons throughout the world, including approximately 2,490 in the United States. None of our U.S.-based employees are represented by unions. We believe that our relations with our employees are generally good.

International Operations

Our international sales of specialty pharmaceutical products have represented 30.9%, 29.6% and 29.4% of total sales for the years ended December 31, 2004, 2003 and 2002, respectively. Our products are sold in over 100 countries. Marketing activities are coordinated on a worldwide basis, and resident management teams provide leadership and infrastructure for customer-focused, rapid introduction of new products in the local markets.

Sales and Marketing

We maintain a global marketing team, as well as regional sales and marketing organizations. We also engage contract sales organizations to promote certain products. Our sales efforts and promotional activities are primarily aimed at eye care professionals, neurologists, plastic surgeons and dermatologists who use, prescribe and recommend our products. We advertise in professional journals and have an extensive direct mail program of descriptive product literature and scientific information that we provide to specialists in the ophthalmic, dermatological and movement disorder fields. We have developed training modules and seminars to update physicians regarding evolving technology in our products. In 2004, we also utilized direct-to-consumer advertising for our *Botox* ® Cosmetic and *Restasis* ® products.

Our products are sold to drug wholesalers, independent and chain drug stores, pharmacies, commercial optical chains, opticians, mass merchandisers, food stores, hospitals, ambulatory surgery centers and medical practitioners, including ophthalmologists, neurologists, dermatologists, pediatricians and plastic surgeons. As of December 31, 2004, we employed approximately 1,400 sales representatives throughout the world. We also utilize distributors for our products in smaller international markets.

U.S. sales, including manufacturing operations, represented 69.1%, 70.4% and 70.6% of our consolidated product net sales in 2004, 2003 and 2002, respectively. Sales to Cardinal Healthcare for the years ended December 31, 2004, 2003 and 2002 were 14.1%, 14.0% and 14.8%, respectively, of our total consolidated product net sales. Sales to McKesson Drug Company for the years ended December 31, 2004, 2003 and 2002 were 13.0%, 14.2% and 13.3%, respectively, of our total consolidated product net sales. No other country, or single customer, generates over 10% of our total product net sales.

Research and Development

Our global research and development efforts currently focus on eye care, skin care, neuromodulators, and neurology. We also have development programs in genitourinary diseases and gastroenterology. We have a fully integrated pharmaceutical research and development organization with in-house discovery programs, including medicinal chemistry, high throughput screening, and biological sciences. We supplement our own research and development activities with our commitment to identify and obtain new technologies through in-licensing, research collaborations, joint ventures and acquisitions.

As of December 31, 2004, we had approximately 1,030 employees involved in our research and development efforts. Our research and development expenditures for 2004, 2003 and 2002 were approximately $345.6 million, $763.5 million and $233.1 million, respectively, including expenditures on in-process research and development in connection with our 2003 acquisitions of Bardeen Sciences Company, LLC and Oculex Pharmaceuticals, Inc. Excluding in-process research and development expenditures, we have increased our annual investment in research and development by over $200 million in the past five years, dedicating approximately 20% of our investment in research and development to the discovery of new compounds. In 2004, we completed construction of a new $75 million research and development facility in Irvine, California, which will provide us with approximately 175,000 square feet of additional laboratory space. In 2004, we began

construction on a new biologics facility on our Irvine, California campus. We expect that this facility will be completed in 2005 at an aggregate cost of approximately $50 million.

Our strategy is to develop innovative products to address unmet medical needs. Our top priorities include furthering our leadership in the field of neuromodulators, identifying new potential compounds for sight-threatening diseases such as glaucoma, age-related macular degeneration and macular edema, and developing novel therapies for pain, gastroenterology, and genitourinary diseases. We plan to continue to build on our strong market positions in therapeutic dry eye products and dermatology products for acne and psoriasis, and to explore new therapeutic areas that are consistent with our specialty pharmaceutical focus.

Eye Care Research and Development. Our research and development efforts for the ophthalmic pharmaceuticals business focus primarily on new therapeutic products for retinal disease, glaucoma, and dry eye. As part of our focus on diseases of the retina, we acquired Oculex Pharmaceuticals, Inc. in 2003. With this acquisition, we obtained a novel drug delivery technology for use with compounds to treat diseases, including macular edema and age-related macular degeneration. We have subsequently begun Phase III studies for macular edema associated with diabetes and retinal vein occlusion. In April 2004, we announced that we were also selected as a partner to supply our novel ophthalmic formulation of triamcinolone for two National Eye Institute-sponsored clinical trials on macular edema associated with diabetic retinopathy and retinal vein occlusion. Under the terms of the clinical trial agreement, we are responsible for all costs associated with drug development, manufacturing, pharmacokinetic studies, and regulatory aspects of the trials. In addition, we will pay a fee to the study coordinating centers for the conduct of the trials.

Neuromodulator Research and Development. We continue to invest heavily in the research and development of neuromodulators, primarily *Botox* ®. We are focused on both expanding the approved indications for *Botox* ® and pursuing new neuromodulator-based therapeutics. This includes expanding the approved uses for *Botox* ® to include treatment for spasticity, headache, brow furrow and urologic conditions including overactive bladder. In collaboration with the United Kingdom's Health Protection Agency, formerly known as the Centre for Applied Microbiology & Research, we are focused on engineering neuromodulators for the treatment of severe pain. We are also continuing our investment in the areas of biologic process development and manufacturing.

Skin Care Research and Development. Our research and development team for our skin care business is working on expanding indications and formulations for tazarotene. As mentioned above, we filed a New Drug Application with the FDA in November 2003 for oral tazarotene for the treatment of moderate to very severe psoriasis. In July 2004, the FDA Joint Dermatologic & Opthalmic Drugs and Drug Safety & Risk Management Advisory Committee recommended against approval of this New Drug Application, and in September 2004, the FDA issued a non-approvable letter. The FDA listed three non-approvability issues for oral tazarotene for the treatment of moderate to very severe psoriasis: (1) the development of an acceptable risk management program; (2) completion of a non-inferiority study in severe psoriasis; and (3) satisfaction of an FDA deficiency letter regarding the manufacture of the oral tazarotene capsules. We intend to continue working with the FDA toward our goal of bringing oral tazarotene to patients suffering from psoriasis.

In November 2002, we entered into a research collaboration and license agreement with Peplin Biotech Ltd. for the right to develop and commercialize PEP005 for the topical treatment of non-melanoma skin cancer and actinic keratosis. In June 2004, we filed Investigational New Drug Applications with the FDA for a topical formulation of PEP005 for the treatment of actinic keratosis, a pre-cancerous skin condition, and for basal cell carcinoma, the most common form of non-melanoma skin cancer. In October 2004, we mutually agreed with Peplin to discontinue our collaboration.

Other Areas of Research and Development. We are also working to leverage our technologies in therapeutic areas outside of our current specialties, such as the use of alpha agonists for the treatment of neuropathic pain. Additionally, we are developing a novel proton pump inhibitor designed to reduce excess stomach acid secretion. In support of these two programs, we filed Investigational New Drug Applications with the FDA for a proton pump inhibitor pro drug for the treatment of gastrointestinal disease in June 2004 and for an alpha adrenergic agonist for the treatment of neuropathic pain in September 2004. These Investigational New Drug Applications remain pending.

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In December 2002, we entered into a strategic research collaboration and license agreement with ExonHit Therapeutics. The goals of this collaboration are to identify new molecular targets based on ExonHit Therapeutics' gene profiling *DATAS* ™ technology and to work collaboratively developing unique compounds and commercial products based on these targets. Our strategic alliance with ExonHit Therapeutics provides us with the rights to compounds developed in the fields of neurodegenerative disease, pain and ophthalmology.

The continuing introduction of new products supplied by our research and development efforts and in-licensing opportunities are critical to our success. There are intrinsic uncertainties associated with research and development efforts and the regulatory process. We cannot assure you that any of the research projects or pending drug marketing approval applications will result in new products that we can commercialize. Delays or failures in one or more significant research projects and pending drug marketing approval applications could have a material adverse affect on our future operations.

Manufacturing

We manufacture the majority of our commercial products in our own plants located in Waco, Texas; Westport, Ireland; and Sao Paulo, Brazil. We maintain sufficient manufacturing capacity at these facilities to support forecasted demand as well as a modest safety margin of additional capacity to meet peaks of demand and sales growth in excess of expectations. We increase our capacity as required in anticipation of future sales increases. In the event of a very large or very rapid unforeseen increase in market demand for a specific product or technology, supply of that product or technology could be negatively impacted until additional capacity is brought on line. Third parties manufacture a small number of commercial products for us. However, the revenues from these products are not material to our operating results.

We are vertically integrated into the production of plastic parts and produce our own bottles, tips and caps for use in the manufacture of our ophthalmic solutions. Additionally, we ferment, purify and characterize the botulinum toxin used in our product *Botox* ®. With these two exceptions, we purchase all other raw materials from qualified domestic and international sources. These raw materials consist of active pharmaceutical ingredients, pharmaceutical excipients, and packaging components. Where practical, we maintain more than one supplier for each material, and we have an ongoing alternate sourcing endeavor that identifies additional sources of key raw materials. In some cases, however, most notably with active pharmaceutical ingredients, we are a niche purchaser of specialty chemicals, which are sole sourced. These sources are identified in filings with regulatory agencies, including the FDA, and cannot be changed without prior regulatory approval. In these cases, we maintain inventories of the raw material itself and precursor intermediates to mitigate the risk of interrupted supply. A lengthy interruption of the supply of one of these materials could adversely affect our ability to manufacture and supply commercial product. A small number of the raw materials required to manufacture certain of our products are derived from biological sources which could be subject to contamination and recall by their suppliers. We use multiple lots of these raw materials at any one time in order to mitigate such risks. However, a shortage, contamination or recall of these products could disrupt our ability to maintain an uninterrupted commercial supply of our finished goods.

Competition

We face significant competition in all of our markets worldwide. Numerous companies are engaged in the development, manufacture and marketing of health care products competitive with those that we manufacture. Our major eye care competitors include Alcon Laboratories, Inc., Bausch & Lomb, Pfizer, Novartis Ophthalmics and Merck & Co., Inc. These competitors have equivalent or, in most cases, greater resources than us. This enables them, among other things, to spread their research and development costs, as well as their marketing and promotion costs, over a broader revenue base. Our competitors may also have more experience and expertise in obtaining marketing approvals from the FDA and other regulatory agencies. Our skin care business competes against a number of companies, including among others, Dermik, a division of Sanofi-Aventis, Galderma, a joint venture between Nestle and L'Oreal, Medicis, Bristol-Myers Squibb, Schering-Plough Corporation and Johnson & Johnson, most of which have greater resources than us. With respect to neuromodulators, until December 2000, *Botox* ® was the only neuromodulator approved by the FDA. At that time, the FDA approved *Myobloc* ®, a neuromodulator formerly marketed by Elan Pharmaceuti-

cals and now marketed by Solstice Neurosciences Inc. We believe that Beaufour Ipsen Ltd. intends to seek FDA approval of its *Dysport* ® neuromodulator for certain therapeutic indications, and that Beaufour Ipsen's marketing partner, Inamed Corporation, intends to seek FDA approval of *Dysport* ®/ *Reloxin* ® for cosmetic indications. Beaufour Ipsen has marketed *Dysport* ® in Europe since 1991, prior to our European commercialization of *Botox* ® in 1992. Also, Mentor Corporation has announced its intention to develop and seek regulatory approval to market a competing neuromodulator in the United States. In addition, we are aware of competing neuromodulators currently being developed and commercialized in Asia, Europe, South America and other markets. A Chinese entity received approval to market a botulinum toxin in China in 1997, and we believe that it has launched or is planning to launch its botulinum toxin product in other lightly regulated markets in Asia, South America and Central America. These lightly regulated markets may not require adherence to the FDA's current good manufacturing practices, or cGMPs, the European Medical Evaluation Agency or other regulatory agencies in countries that are members of the Organization for Economic Cooperation and Development, and companies operating in these markets may be able to produce products at a lower cost than we can. In addition, Merz Pharmaceuticals is seeking German regulatory approval for a botulinum toxin currently expected to be launched during the second half of 2005, and a Korean company is developing a botulinum toxin that received exportation approval from Korean authorities in early 2005 and that is expected to be launched in Korea during 2005.

In addition, competition from generic drug manufacturers is a major challenge in the United States and is growing internationally. In marketing our products to health care professionals, pharmacy benefits management companies, health care maintenance organizations, and various other national and regional health care providers and managed care entities, we compete primarily on the basis of product quality, product technology, price, reputation and access to technical information. We believe that we compete favorably in our product markets.

Government Regulation

Cosmetics, drugs and biologics are subject to regulation by the FDA, state agencies and, in varying degrees, by foreign health agencies. Pharmaceutical products and biologics are subject to extensive pre- and post-market regulation by the FDA, including regulations that govern the testing, manufacturing, safety, efficacy, labeling, storage, record keeping, advertising and promotion of the products under the Federal Food, Drug, and Cosmetic Act with respect to drugs and the Public Health Services Act with respect to biologics, and by comparable agencies in a number of foreign countries. Failure to comply with applicable FDA or other requirements may result in civil or criminal penalties, recall or seizure of products, partial or total suspension of production or withdrawal of a product from the market.

The process required by the FDA before a new drug or biologic may be marketed in the United States generally involves the following: completion of preclinical laboratory and animal testing; submission of an Investigational New Drug Application, which must become effective before clinical trials may begin; and performance of adequate and well controlled human clinical trials to establish the safety and efficacy of the proposed drug or biologic for its intended use. Clinical trials are typically conducted in three sequential phases, which may overlap, and must satisfy extensive Good Clinical Practice regulations and regulations for informed consent. Approval by the FDA of a New Drug Application, or NDA, is required prior to marketing a new drug, and approval of a Biologics License Application, or BLA, is required before a biologic may be legally marketed in the United States. To satisfy the criteria for approval, an NDA or BLA must demonstrate the safety and effectiveness of the product based on results of product development, preclinical studies and the three phases of clinical trials. Both NDAs and BLAs must also contain extensive manufacturing information, and the applicant must pass an FDA pre-approval inspection of the manufacturing facilities at which the drug or biologic is produced to assess compliance with the FDA's current good manufacturing practices, or cGMPs, prior to commercialization. Satisfaction of FDA pre-market approval requirements typically takes several years and the actual time required may vary substantially based on the type, complexity and novelty of the product, and we cannot be certain that any approvals for our products will be granted on a timely basis, or at all.

Once approved, the FDA may withdraw product approval if compliance with pre- and post-market regulatory standards is not maintained or if safety problems occur after the product reaches the marketplace. In addition, the FDA may require post-marketing clinical studies and surveillance programs to monitor the effect of approved products. The FDA may limit further marketing of the product based on the results of these post-market studies and programs. Drugs and biologics may be marketed only for the approved indications and in accordance with the provisions of the approved label. Further, any modifications to the drug or biologic, including changes in indications, labeling, or manufacturing processes or facilities, may require the submission of a new or supplemental NDA or BLA, which may require that we develop additional data or conduct additional preclinical studies and clinical trials.

Any products manufactured or distributed by us or our collaborators pursuant to FDA approvals are also subject to continuing regulation by the FDA, including recordkeeping requirements and reporting of adverse experiences associated with the drug. Drug and biologic manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMPs, which regulate all aspects of the manufacturing process and impose certain procedural and documentation requirements. Failure to comply with the statutory and legal requirements can subject a manufacturer to possible legal or regulatory action, including fines and civil penalties, suspension or delay in the issuance of approvals, seizure or recall of products, and withdrawal of approvals, any one or more of which could have a material adverse effect upon us.

The FDA imposes a number of complex regulatory requirements on entities that advertise and promote pharmaceuticals and biologics, including, but not limited to, standards and regulations for direct-to-consumer advertising, off-label promotion, industry sponsored scientific and educational activities, and promotional activities involving the Internet. A manufacturer can make only those claims relating to safety and efficacy that are approved by the FDA. The FDA has very broad enforcement authority under the Federal Food, Drug, and Cosmetic Act, and failure to abide by these regulations can result in penalties, including the issuance of a warning letter directing us to correct deviations from FDA standards, a requirement that future advertising and promotional materials be pre-cleared by the FDA, and state and federal civil and criminal investigations and prosecutions. Physicians may prescribe legally available drugs and biologics for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use.

We are also subject to various laws and regulations regarding laboratory practices, the experimental use of animals, and the use and disposal of hazardous or potentially hazardous substances in connection with our research. In each of these areas, as above, the FDA has broad regulatory and enforcement powers, including the ability to levy fines and civil penalties, suspend or delay the issuance of approvals, seize or recall products, and withdraw approvals, any one or more of which could have a material adverse effect upon us.

Internationally, the regulation of drugs is also complex. In Europe, our products are subject to extensive regulatory requirements. As in the United States, the marketing of medicinal products has for many years been subject to the granting of marketing authorizations by medicine agencies. Particular emphasis is also being placed on more sophisticated and faster procedures for reporting adverse events to the competent authorities. The European Union procedures for the authorization of medicinal products were amended in May 2004 and are due to be implemented by October 2005. The new procedures are intended to improve the efficiency of operation of both the mutual recognition and centralized procedures. Additionally, new rules have been introduced or are under discussion in several areas, including the harmonization of clinical research laws and the law relating to orphan drugs and orphan indications. Outside the United States, reimbursement pricing is typically regulated by government agencies.

Among other countries, we currently sell *Botox* ® in Japan, where the regulatory process is at least as equally complex as in the U.S. Pre-marketing approval and clinical studies are required, as is negotiated

governmental pricing for pharmaceuticals. The regulatory regime for pharmaceuticals in Japan has historically been lengthy and costly, primarily because Japan required the repetition of all relevant clinical studies in Japan. Japan is in the process of implementing changes to comply with the International Conference on Harmonization, an agreement among Japan, the United States and the European Union to facilitate the registration of drugs utilizing data collected outside of the country. The timeline for completion of these changes and the rules during this transitional period are not certain. During this transitional period, registration of pharmaceutical products will remain unpredictable.

The total cost of providing health care services has been and will continue to be subject to review by governmental agencies and legislative bodies in the major world markets, including the United States, which are faced with significant pressure to lower health care costs. The Medicare Prescription Drug Modernization Act of 2003 imposed certain reimbursement restrictions on our products in the United States. These reimbursement restrictions or other price reductions or controls could materially and adversely affect our revenues and financial condition. Additionally, price reductions and rebates have recently been mandated in several European countries, principally Germany, Italy, Spain and the United Kingdom. Certain products are also no longer eligible for reimbursement in France, Italy and Germany. Reference pricing is used in several markets around the world to reduce prices. Furthermore, parallel trade within the European Union, whereby products flow from relatively low-priced to high-priced markets, has been increasing.

We cannot predict the likelihood or pace of any significant regulatory or legislative action in these areas, nor can we predict whether or in what form health care legislation being formulated by various governments will be passed. Medicare reimbursement rates are subject to change at any time. We also cannot predict with precision what effect such governmental measures would have if they were ultimately enacted into law. However, in general, we believe that such legislative activity will likely continue. If adopted, such measures can be expected to have an impact on our business.

Patents, Trademarks and Licenses

We own, or are licensed under, numerous U.S. and foreign patents relating to our products, product uses and manufacturing processes. We believe that our patents and licenses are important to our business, but that with the exception of the U.S. and European patents relating to *Lumigan* ®, *Acular* ® and *Alphagan* ® *P*, no one patent or license is currently of material importance in relation to our overall sales. The U.S. compound and ophthalmic use patents covering *Lumigan* ® currently expire in 2012. An application is pending with the U.S. Patent and Trademark Office for a patent term extension for *Lumigan* ®. The European patent covering *Lumigan* ® expires in various countries between 2013 and 2017. The U.S. patent covering the commercial formulation of *Acular* ® expires in 2009; and in 2008 in Europe. The U.S. patents covering the commercial formulation of *Alphagan* ® *P* expire in 2012 and 2021; and in 2009 in Europe, with corresponding patents pending.

Our success with our products will depend, in part, on our ability to obtain, and successfully defend if challenged, patent or other proprietary protection. However, the issuance of a patent is not conclusive as to its validity or as to the enforceable scope of the claims of the patent. Accordingly, our patents may not prevent other companies from developing similar or functionally equivalent products or from successfully challenging the validity of our patents. Hence, if our patent applications are not approved or, even if approved, such patents are circumvented or not upheld in a legal proceeding, our ability to competitively exploit our patented products and technologies may be significantly reduced. Also, such patents may or may not provide competitive advantages for their respective products or they may be challenged or circumvented by competitors, in which case our ability to commercially exploit these products may be diminished.

From time to time, we may need to obtain licenses to patents and other proprietary rights held by third parties to develop, manufacture and market our products. If we are unable to timely obtain these licenses on commercially reasonable terms, our ability to commercially exploit such products may be inhibited or prevented. See "Certain Factors and Trends Affecting Allergan and its Businesses — We may be subject to intellectual property litigation and infringement claims, which could cause us to incur significant expenses and losses or prevent us from selling our products."

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We also rely on trade secrets and proprietary know-how that we seek to protect, in part, through confidentiality agreements with our partners, customers, employees and consultants. It is possible that these agreements will be breached or will not be enforceable in every instance, and that we will not have adequate remedies for any such breach. It is also possible that our trade secrets will otherwise become known or independently developed by competitors.

We may find it necessary to initiate litigation to enforce our patent rights, to protect our trade secrets or know-how or to determine the scope and validity of the proprietary rights of others. Litigation involving patents, trademarks, copyrights and proprietary technologies can often be protracted and expensive and, as with litigation generally, the outcome is inherently uncertain. See Item 3 of Part I of this report, "Legal Proceedings" and Note 13, "Commitments and Contingencies," in the notes to the consolidated financial statements listed under Item 15(a) of Part IV of this report for information concerning our current intellectual property litigation.

We market our products under various trademarks, for which we have both registered and unregistered trademark protection in the United States and certain countries outside the United States. We consider these trademarks to be valuable because of their contribution to the market identification of our products.

Environmental Matters

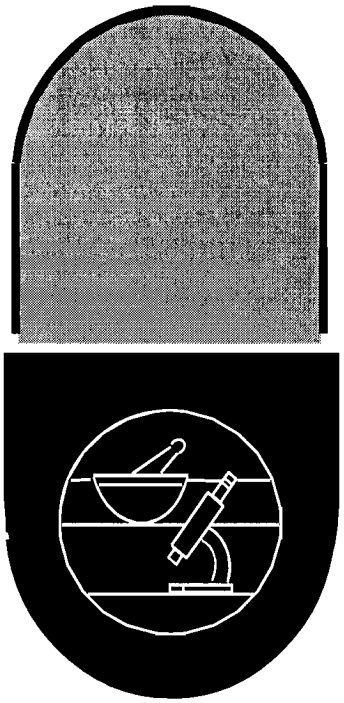
We are subject to federal, state, local and foreign environmental laws and regulations. We believe that our operations comply in all material respects with applicable environmental laws and regulations in each country where we have a business presence. Although we continue to make capital expenditures for environmental protection, we do not anticipate any significant expenditures in order to comply with such laws and regulations that would have a material impact on our earnings or competitive position. We are not aware of any pending litigation or significant financial obligations arising from current or past environmental practices that are likely to have a material adverse effect on our financial position. We cannot assure you, however, that environmental problems relating to properties owned or operated by us will not develop in the future, and we cannot predict whether any such problems, if they were to develop, could require significant expenditures on our part. In addition, we are unable to predict what legislation or regulations may be adopted or enacted in the future with respect to environmental protection and waste disposal.

Seasonality

Our business, taken as a whole, is not materially affected by seasonal factors, although we have noticed an historical trend with respect to sales of our *Botox* ® product. Specifically, sales of *Botox* ® have tended to be lowest during the first fiscal quarter, with sales during the second and third fiscal quarters being comparable and marginally higher than sales during the first fiscal quarter. *Botox* ® sales during the fourth fiscal quarter have tended to be the highest due to patients obtaining their final therapeutic treatment at the end of the year, presumably to fully utilize deductibles and to receive additional cosmetic treatments prior to the holiday season.

CERTAIN FACTORS AND TRENDS AFFECTING ALLERGAN AND ITS BUSINESSES

Statements made by us in this report and in other reports and statements released by us that are not historical facts constitute "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, Section 21 of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. These forward-looking statements are necessarily estimates reflecting the best judgment of senior management and include comments that express our opinions about trends and factors that may impact future operating results. Disclosures that use words such as we "believe," "anticipate," "estimate," "intend," "could," "plan," "expect" and similar expressions are intended to identify forward-looking statements. Such statements rely on a number of assumptions concerning future events, many of which are outside of our control, and involve risks and uncertainties that could cause actual results to differ materially from opinions and expectations. Any such forward-looking statements, whether made in this report or elsewhere, should be considered in context of the various disclosures made by us about our businesses including, without limitation,



APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

28th EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2008

BIVALIRUDIN

INJECTABLE; INTRAVENOUS

ANGIOMAX

	+	MEDICINES CO	250MG/VIAL	N20873	001	Dec 15, 2000

BLEOMYCIN SULFATE

INJECTABLE; INJECTION

BLENOXANE

AP	+	BRISTOL MYERS SQUIBB	EQ 15 UNITS BASE/VIAL	N50443	001	
AP	+		EQ 30 UNITS BASE/VIAL	N50443	002	Sep 07, 1995

BLEOMYCIN

AP		BEDFORD	EQ 15 UNITS BASE/VIAL	N65042	002	Oct 17, 2001
AP			EQ 30 UNITS BASE/VIAL	N65042	001	Oct 17, 2001
AP		HOSPIRA	EQ 15 UNITS BASE/VIAL	N65031	001	Mar 10, 2000
AP			EQ 30 UNITS BASE/VIAL	N65031	002	Mar 10, 2000
AP		PHARMACHEMIE BV	EQ 15 UNITS BASE/VIAL	N65201	001	Dec 13, 2007
AP		TEVA PARENTERAL	EQ 15 UNITS BASE/VIAL	N65033	001	Jun 27, 2000
AP			EQ 30 UNITS BASE/VIAL	N65033	002	Jun 27, 2000

BORTEZOMIB

INJECTABLE; INTRAVENOUS

VELCADE

	+	MILLENNIUM PHARMS	3.5MG/VIAL	N21602	001	May 13, 2003

BOSENTAN

TABLET; ORAL

TRACLEER

		ACTELION	62.5MG	N21290	001	Nov 20, 2001
	+		125MG	N21290	002	Nov 20, 2001

BRETYLIUM TOSYLATE

INJECTABLE; INJECTION

BRETYLIUM TOSYLATE

AP	+	INTL MEDICATION	50MG/ML	N70119	001	Apr 29, 1986
AP		LUITPOLD	50MG/ML	N70891	001	Jul 26, 1988

BRETYLIUM TOSYLATE IN DEXTROSE 5% IN PLASTIC CONTAINER

AP	+	B BRAUN	200MG/100ML	N19121	002	Apr 29, 1986
AP	+		400MG/100ML	N19121	003	Apr 29, 1986
AP	+	HOSPIRA	200MG/100ML	N19008	002	Apr 29, 1986
AP	+		400MG/100ML	N19008	003	Apr 29, 1986

BRETYLIUM TOSYLATE IN PLASTIC CONTAINER

AP	+	HOSPIRA	50MG/ML	N19030	001	Apr 29, 1986

BRETYLIUM TOSYLATE IN DEXTROSE 5% IN PLASTIC CONTAINER

	+	B BRAUN	100MG/100ML	N19121	001	Apr 29, 1986

BRIMONIDINE TARTRATE

SOLUTION/DROPS; OPHTHALMIC

ALPHAGAN P

AT	+	ALLERGAN	0.15%	N21262	001	Mar 16, 2001

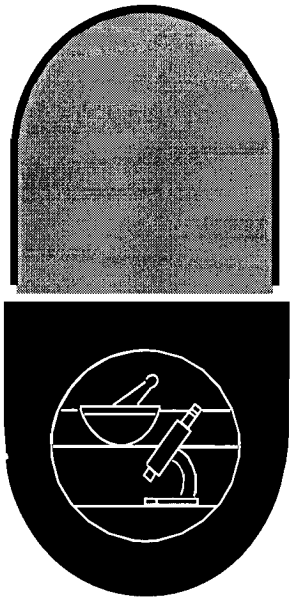
BRIMONIDINE TARTRATE

AT		AKORN	0.2%	N76439	001	Mar 14, 2006
AT		ALCON	0.2%	N76254	001	Sep 16, 2003
AT		ALCON RES	0.15%	N21764	001	May 22, 2006
AT	+	BAUSCH AND LOMB	0.2%	N76260	001	May 28, 2003
AT		IVAX PHARMS	0.2%	N76372	001	Sep 10, 2004

ALPHAGAN P

	+	ALLERGAN	0.1%	N21770	001	Aug 19, 2005

CUMULATIVE SUPPLEMENT 04
April 2008



APPROVED DRUG PRODUCTS

WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

28th EDITION

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs

2008

BENZONATATE

CAPSULE; ORAL

BENZONATATE

AA	ORIT LABS LLC	100MG	N40682	001	Jul 30, 2007	Jan	CAHN
AA		200MG	N40682	002	Jul 30, 2007	Jan	CAHN
AA	SUN PHARM INDS INC	100MG	N40587	001	Mar 19, 2008	Mar	NEWA
AA		200MG	N40587	002	Mar 19, 2008	Mar	NEWA

BENZTHIAZIDE

TABLET; ORAL

BENZTHIAZIDE

>D>	@ LEINER	50MG	N83206	001		Apr	CAHN
>A>	@ PVT FORM	50MG	N83206	001		Apr	CAHN

BENZTROPINE MESYLATE

TABLET; ORAL

BENZTROPINE MESYLATE

AA	ACTAVIS TOTOWA	0.5MG	N40699	001	Feb 14, 2008	Jan	NEWA
AA		1MG	N40705	001	Feb 14, 2008	Jan	NEWA
AA		2MG	N40706	001	Feb 14, 2008	Jan	NEWA
	@ MUTUAL PHARM	1MG	N81264	001	Jan 23, 1992	Feb	DISC
	@	2MG	N81265	001	Jan 23, 1992	Feb	DISC

BETHANECHOL CHLORIDE

TABLET; ORAL

BETHANECHOL CHLORIDE

AA	LANNETT	5MG	N40703	001	Mar 27, 2008	Mar	NEWA
AA		10MG	N40704	001	Mar 27, 2008	Mar	NEWA
AA		25MG	N40678	003	Mar 27, 2008	Mar	NEWA
AA		50MG	N40677	001	Mar 27, 2008	Mar	NEWA

BLEOMYCIN SULFATE

INJECTABLE; INJECTION

BLEOMYCIN SULFATE

AP	ABRAXIS PHARM	EQ 15 UNITS BASE/VIAL	N65185	001	Jan 28, 2008	Jan	NEWA
AP		EQ 30 UNITS BASE/VIAL	N65185	002	Jan 28, 2008	Jan	NEWA
AP	BEDFORD	EQ 15 UNITS BASE/VIAL	N65042	002	Oct 17, 2001	Jan	CTNA
AP		EQ 30 UNITS BASE/VIAL	N65042	001	Oct 17, 2001	Jan	CTNA
AP	HOSPIRA	EQ 15 UNITS BASE/VIAL	N65031	001	Mar 10, 2000	Jan	CTNA
AP		EQ 30 UNITS BASE/VIAL	N65031	002	Mar 10, 2000	Jan	CTNA
AP	PHARMACHEMIE BV	EQ 15 UNITS BASE/VIAL	N65201	001	Dec 13, 2007	Jan	CTNA
AP	TEVA PARENTERAL	EQ 15 UNITS BASE/VIAL	N65033	001	Jun 27, 2000	Jan	CTNA
AP		EQ 30 UNITS BASE/VIAL	N65033	002	Jun 27, 2000	Jan	CTNA

BRIMONIDINE TARTRATE

SOLUTION/DROPS; OPHTHALMIC

BRIMONIDINE TARTRATE

AT	SANDOZ	0.2%	N78075	001	Jan 30, 2008	Jan	NEWA

BROMODIPHENHYDRAMINE HYDROCHLORIDE; CODEINE PHOSPHATE

SYRUP; ORAL

BROMODIPHENHYDRAMINE HYDROCHLORIDE AND CODEINE PHOSPHATE

	@ MORTON GROVE	12.5MG/5ML;10MG/5ML	N88626	001	Oct 12, 1984	Feb	DISC

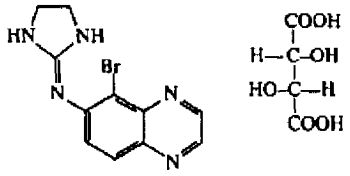
ALPHAGAN® P

(brimonidine tartrate ophthalmic solution) 0.15%

STERILE

DESCRIPTION

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white to pale yellow powder. It has a molecular weight of 442.24 as the tartrate salt, and is both soluble in water (1.5 mg/mL) and in the product vehicle (3.0 mg/mL) at pH 7.2. The structural formula is:



Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$
CAS Number: 59803-98-4

In solution, **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.15% has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 6.6-7.4.

Each mL of **ALPHAGAN® P** contains:
Active ingredient: brimonidine tartrate 0.15% (1.5 mg/mL)
Preservative: Purite® 0.005% (0.05 mg/mL)
Inactives: boric acid; calcium chloride; magnesium chloride; potassium chloride; purified water; sodium borate; sodium carboxymethylcellulose; sodium chloride; with hydrochloric acid and/or sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of Action: **ALPHAGAN® P** is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacokinetics: After ocular administration of either a 0.1% or 0.2% solution, plasma concentrations peaked within 0.5 to 2.5 hours and declined with a systemic half-life of approximately 2 hours. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

Clinical Evaluations: Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

Two clinical studies were conducted to evaluate the safety, efficacy, and acceptability of **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.15% compared with **ALPHAGAN®** administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. Those results indicated that **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.15% is comparable in IOP lowering effect to **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-5 mm Hg.

INDICATIONS AND USAGE

ALPHAGAN® P is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

ALPHAGAN® P is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS

General: Although **ALPHAGAN® P** had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

ALPHAGAN® P has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

ALPHAGAN® P should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients: As with other drugs in this class, **ALPHAGAN® P** may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Drug Interactions: Although specific drug interaction studies have not been conducted with **ALPHAGAN® P**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), anti-hypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **ALPHAGAN® P** in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after **ALPHAGAN® P** administration are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved 86 and 55 times, respectively, the plasma drug concentration estimated in humans treated with one drop of **ALPHAGAN® P** into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility due to **ALPHAGAN® P**.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to **ALPHAGAN® P**. Dosing at this level produced an exposure that is 189 times higher than the exposure seen in humans following multiple ophthalmic doses.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. **ALPHAGAN® P** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50% - 83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

The safety and effectiveness of brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years. (Also refer to Adverse Reactions section.)

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

Adverse events occurring in approximately 10-20% of the subjects included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus.

Adverse events occurring in approximately 5-9% of the subjects included: burning sensation, conjunctival folliculosis, hypertension, oral dryness, and visual disturbance.

Events occurring in approximately 1-4% of subjects included: allergic reaction, asthenia, blepharitis, bronchitis, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, flu syndrome, follicular conjunctivitis, foreign body sensation, headache, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, stinging, superficial punctate keratopathy, visual field defect, vitreous floaters, and worsened visual acuity.

The following events were reported in less than 1% of subjects: corneal erosion, insomnia, nasal dryness, somnolence, and taste perversion.

The following events have been identified during post-marketing use of **ALPHAGAN®** in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ALPHAGAN®**, or a combination of these factors, include: bradycardia; hypotension; iritis; miosis; skin reactions (including erythema, eyelid pruritus, rash, and vasodilation) and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving **ALPHAGAN®**.

OVERDOSAGE

No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of **ALPHAGAN® P** in the affected eye(s) three times daily, approximately 8 hours apart.

ALPHAGAN® P may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

HOW SUPPLIED

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% is supplied sterile in opaque teal LDPE plastic bottles and tips with purple high impact polystyrene (HIPS) caps as follows:

5 mL in 10 mL bottle	NDC 0023-9177-05
10 mL in 10 mL bottle	NDC 0023-9177-10
15 mL in 15 mL bottle	NDC 0023-9177-15

NOTE: Store between 15°-25° C (59°-77°F).

Rx Only

ALLERGAN

US Patent Nos. 5,424,078; 5,736,165
Revised December 2001
7831X

Alphagan P
(brimonidine tartrate ophthalmic solution) 0.15%

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UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

WESTERN DIVISION

ALLERGAN, INC.,

Plaintiff,

v.

EXELA PHARMSCI, INC.; EXELA PHARMSCI PVT., LTD., PADDOCK LABORATORIES, INC., and PHARMAFORCE, INC.,

Defendants.

Case No. CV07-01967 R (RCx)

AMENDED COMPLAINT FOR PATENT INFRINGEMENT

JURY TRIAL DEMANDED

Honorable Manuel L. Real
Courtroom 8

FILE BY FAX

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Allergan, Inc. ("Allergan" or "Plaintiff"), by its attorneys, for its complaint against Defendants Exela PharmSci, Inc. ("Exela U.S."), Exela PharmSci PVT., Ltd., Inc. ("Exela India") (collectively, "Exela"), Paddock Laboratories, Inc. ("Paddock"), and PharmaForce, Inc. ("PharmaForce") (all four entities collectively "Defendants") alleges as follows:

The Nature of the Action

1. This is an action for infringement of United States Patent No. 6,641,834 (the "'834 patent") under 35 U.S.C. §§ 271(e)(2) and 271(b), and for a declaratory judgment of infringement of the '834 Patent under 28 U.S.C. §§ 2201 and 2202. A copy of the '834 patent is attached as Exhibit A. This Court has subject matter jurisdiction over the action under 28 U.S.C. §§ 1331, 1338, 2201, and 2202.

The Parties

2. Plaintiff Allergan is a corporation organized and existing under the laws of the State of Delaware, with its worldwide headquarters at 2525 Dupont Drive, Irvine, California 92612. Allergan employs over 2,000 people in the State of California, and directs the marketing, manufacture and sale of its commercially successful glaucoma drug, ALPHAGAN® P 0.15% brimonidine tartrate ophthalmic solution, from its offices there. Allergan has been and will be injured by the acts complained of herein.

3. On information and belief, Defendant Exela PharmSci, Inc. ("Exela U.S.") is an entity organized under the laws of the State of Virginia, and is headquartered at 11710 Plaza America Dr., Suite 2000, Reston, VA 20190. On information and belief, Exela U.S. has only four shareholders.

4. On information and belief, Defendant Exela PharmSci PVT., Ltd. ("Exela India") is an entity organized under the laws of the country of India with headquarters at # 139/1 Saptagiri, Sarwabowma Nagar, Bilekahalli, Bannerghatta Road, Bangalore, Karnataka, India, 560076.

5. On information and belief, Exela India and Exela U.S. are alter egos of one another or agents of one another as it relates to the actions complained of herein.

6. On information and belief, Exela India and Exela U.S. share the same Internet website, http://www.exela.com. This website lists a California resident and address for its administrative contact: Exela, smccormack@neurosystec.com, 746 Gettysburg Circle, Claremont, CA 91711, United States, Phone: (909) 621-2994.

7. U.S. Trademark Applications filed for the mark "EXELA PHARMSCI" have listed either a California or Indian address for the applicant. The California address is for a Mr. Phanesh Koneru, 3053 Bighorn Drive, Corona, California 92881. On information and belief, Mr. Koneru is the Chief Executive Officer of Exela U.S., and is the person who signed a letter notifying Allergan of an Abbreviated New Drug Application ("ANDA") filing for a generic version of Allergan's ALPHAGAN® P product, as further described in paragraphs 22 through 24.

8. Exela also maintains a website that is "under construction" at http://www.exela.us. The registration for this website is held by Mr. Koneru at 3053 Bighorn Drive, Corona, California 92881, with two phone numbers listed, one with a California area code at 951-898-5960, and the other with a Virginia area code at 703-964-7994.

9. On information and belief, Mr. Koneru is the sole employee of Exela U.S. On information and belief, the company's phone number is the same as Mr. Koneru's cellular telephone number. On information and belief, Mr. Koneru owns over 80 percent of the stock in Exela U.S.

10. On information and belief, Defendant Paddock Laboratories, Inc. ("Paddock") is a corporation organized and existing under the laws of the State of Minnesota, with its headquarters and principal place of business at 3940 Quebec Avenue North, Minneapolis, Minnesota 55427.

11. According to Exela's Certificate as to Interested Parties Pursuant to Local Rule 7.1-1, filed with this Court on April 16, 2007, Paddock is an "insurer and indemnifier" for Exela in this litigation concerning Defendants' generic version of Allergan's ALPHAGAN® P product. On information and belief, Paddock is not in the business of selling insurance of any kind.

12. Paddock manufactures a variety of different generic pharmaceutical products and sells them throughout the United States, including California.

13. On information and belief, Defendant PharmaForce, Inc. ("PharmaForce") is a corporation organized and existing under the laws of the State of Delaware, with its headquarters and principal place of business at 960 Crupper Avenue, Columbus, Ohio 43229.

14. On information and belief, PharmaForce's registered statutory agent is OSAC, Inc., located at 100 South Third Street, Columbus, Ohio 43215.

15. On information and belief, PharmaForce develops and manufactures a variety of sterile pharmaceutical products.

Jurisdiction and Venue

16. This action arises under the patent laws of the United States of America, United States Code, Title 35, Section 1, *et seq.* This Court has subject matter jurisdiction over the action under 28 U.S.C. §§ 1331, 1338, 2201, and 2202.

17. Based on the facts and causes alleged herein and any other facts to be determined, this Court has personal jurisdiction over Defendants.

18. Venue is proper under 28 U.S.C. §§ 1391 and 1400(b).

Background

19. The '834 patent, entitled "Compositions Containing Alpha-2-Adrenergic Agonist Components," issued to Allergan inventors Orest Olejnik and Edward D.S. Kerslake on November 4, 2003. Allergan owns the '834 patent by assignment.

20. Allergan is the holder of an approved New Drug Application (NDA No. 21-262) for a 0.15% brimonidine tartrate ophthalmic solution sold under the ALPHAGAN® P trademark. In conjunction with NDA No. 21-262, Allergan has listed with the United States Food and Drug Administration ("FDA") five patents (the "Listed Patents") that cover various aspects of the approved formulation of ALPHAGAN® P. One of the Listed Patents is the '834 patent.

21. The research and development work that led to the '834 patent took place at Allergan's facilities in Irvine, California, as did the formulation work for Allergan's ALPHAGAN® P product. In addition, the preparation of NDA No. 21-262 took place at Allergan's facilities in Irvine, California.

22. On February 12, 2007, Allergan received at its Irvine, California offices a letter signed on behalf of Exela by Mr. Phanesh Koneru on Exela PharmSci, Inc. letterhead (the "Paragraph IV Letter"). The telephone number listed on the letter is identified as a "cell" number at 703-964-7994, the same number identified in paragraph 8 above. The e-mail address listed on the letter is at "exela.us," the same domain identified at paragraph 8 above.

23. The stated purpose of the Paragraph IV Letter was to notify Allergan that Exela had filed a certification with the FDA under 21 C.F.R. § 314.50(i)(1)(i)(A)(4) in conjunction with ANDA No. 78-590 filed by Exela for approval of a generic version of Allergan's ALPHAGAN® P product. The Paragraph IV Letter stated that Defendants' generic version of Allergan's ALPHAGAN® P product allegedly would not infringe the Listed Patents and/or that the Listed Patents are invalid.

24. The Paragraph IV Letter contains very limited information about the generic formulation for which Defendants filed ANDA 78-590. For example, the Paragraph IV Letter does not identify all of the ingredients in the product. One or more of the Listed Patents contain claims covering brimonidine tartrate or an alpha-2-agonist such as brimonidine tartrate in combination with other excipients that

could be in Defendants' product.

25. Since receiving the Paragraph IV Letter, Allergan has attempted several times to procure a copy of ANDA 78-590 from Exela. Exela has been unwilling to provide ANDA 78-590 except under conditions that would not allow Allergan to meaningfully process the information contained in the ANDA. In addition, Exela stated in its original offer to provide the ANDA that it would "make no representation or warranty of any kind, whether express or implied, about the accuracy or completeness of the Information" it might provide.

26. Because it has been unable to obtain a copy of ANDA 78-590, Allergan alleges its causes based primarily on the representations contained in the Paragraph IV Letter and the other facts alleged herein.

27. On information and belief, Exela India performed formulation and development work for Defendants' generic version of Allergan's ALPHAGAN® P product at the request of Exela U.S.

28. On information and belief, Exela U.S. took the work Exela India performed and entered into a license agreement with Paddock.

29. On information and belief, as part of the agreement, Paddock agreed to indemnify and insure Exela against all liabilities that might result from the filing of an ANDA for Defendants' generic version of Allergan's ALPHAGAN® P product, including any liabilities or costs associated with this litigation.

30. On information and belief, Paddock enlisted PharmaForce to perform additional formulation and development work for Defendants' generic version of Allergan's ALPHAGAN® P product, manufacture the product, and prepare the ANDA.

31. On information and belief, PharmaForce, acting as agent for Exela and/or Paddock, drafted the ANDA and delivered the ANDA to the FDA's offices in Maryland.

32. In filing their ANDA, Defendants requested the FDA's approval to market a generic version of Allergan's ALPHAGAN® P product throughout the entire United States, including California.

33. On information and belief, under the licensing arrangement between Paddock and Exela, Paddock has the exclusive right to manufacture and market Defendants' generic version of Allergan's ALPHAGAN® P product once the FDA approves ANDA 78-590.

34. On information and belief, Exela and/or Paddock have entered into an agreement with PharmaForce under which PharmaForce will manufacture Defendants' generic version of Allergan's ALPHAGAN® P product once the FDA approves ANDA 78-590.

Count I

(Infringement of the '834 Patent Under 35 U.S.C. § 271(e)(2))

35. Paragraphs 1 to 34 are incorporated herein as set forth above.

36. Defendants, acting jointly, submitted ANDA No. 78-590 to the FDA to obtain approval under the Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a proposed Brimonidine Tartrate Ophthalmic Solution 0.15% product throughout the United States. By submitting the application, Defendants, individually and collectively, committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

37. Exela, acting in concert with the other Defendants, submitted ANDA No. 78-590 to the FDA to obtain approval under the Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a proposed Brimonidine Tartrate Ophthalmic Solution 0.15% product throughout the United States. By submitting the application, Exela has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

38. When Exela submitted ANDA No. 78-590 to the FDA to obtain approval under the Food, Drug, and Cosmetic Act to engage in the commercial

manufacture, use, or sale of a proposed Brimonidine Tartrate Ophthalmic Solution 0.15% product throughout the United States, it was acting jointly with Paddock and/or acting as Paddock's agent. By acting jointly with Exela to submit the application and/or causing its agent to submit the application, Paddock has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

39. When PharmaForce delivered ANDA No. 78-590 to the FDA to obtain approval under the Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a proposed Brimonidine Tartrate Ophthalmic Solution 0.15% product throughout the United States, it was acting as agent for Exela and/or Paddock. By acting as agent for Exela and/or Paddock to submit the application, PharmaForce has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

40. The commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product will infringe the '834 patent.

Count II

(Infringement of the '834 Patent Under 35 U.S.C. § 271(b))

41. Paragraphs 1 to 34 are incorporated herein as set forth above.

42. Exela, acting in concert with the other Defendants, submitted ANDA No. 78-590 to the FDA to obtain approval under the Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a proposed Brimonidine Tartrate Ophthalmic Solution 0.15% product throughout the United States. By submitting the application, Exela has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

43. Paddock actively induced Exela to submit ANDA No. 78-590 to the FDA to obtain approval under the Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a proposed Brimonidine Tartrate Ophthalmic Solution 0.15% product throughout the United States. By actively inducing submission of the ANDA, Paddock has committed an act of indirect

infringement under 35 U.S.C. § 271(b).

44. PharmaForce actively induced Exela to submit ANDA No. 78-590 to the FDA to obtain approval under the Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale of a proposed Brimonidine Tartrate Ophthalmic Solution 0.15% product throughout the United States. By actively inducing submission of the ANDA, PharmaForce has committed an act of indirect infringement under 35 U.S.C. § 271(b).

45. The commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product will infringe the '834 patent.

Count III

(Declaratory Judgment of Infringement of the '834 Patent Under 35 U.S.C. § 271(a))

46. Paragraphs 1 to 34 are incorporated herein as set forth above.

47. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

48. There is an actual case or controversy such that the Court may entertain Allergan's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

49. Defendants have made, and will continue to make, substantial preparation in the United States to manufacture, sell, offer to sell, and/or import Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product.

50. Defendants' actions indicate a refusal to change the course of their actions in the face of acts by Allergan.

51. The commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic

Solution 0.15% product will infringe the '834 patent.

52. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product by any or all of Defendants will infringe the '834 patent.

Prayer For Relief

Plaintiff respectfully prays for the following relief:

a. That judgment be entered that Defendants, individually and/or collectively, have infringed the '834 patent under 35 U.S.C. § 271(e)(2)(A) by submitting ANDA No. 78-590 under the Federal Food Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product will constitute an act of infringement of the '834 patent;

b. That judgment be entered that Exela has infringed the '834 patent under 35 U.S.C. § 271(e)(2)(A) by submitting ANDA No. 78-590 under the Federal Food Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product will constitute an act of infringement of the '834 patent;

c. That judgment be entered that Paddock has infringed the '834 patent under 35 U.S.C. § 271(e)(2)(A) by acting jointly with Exela or allowing Exela to act as its agent in submitting ANDA No. 78-590 under the Federal Food Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product will constitute an act of infringement of the '834 patent;

d. That judgment be entered that PharmaForce has infringed the '834 patent under 35 U.S.C. § 271(e)(2)(A) by acting as agent for Exela and/or Paddock in submitting ANDA No. 78-590 under the Federal Food Drug, and Cosmetic Act,

and that the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product will constitute an act of infringement of the '834 patent;

e. That judgment be entered that Paddock has infringed the '834 patent under 35 U.S.C. § 271(b) by inducing Exela to submit ANDA No. 78-590 under the Federal Food Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product will constitute an act of infringement of the '834 patent;

f. That judgment be entered that PharmaForce has infringed the '834 patent under 35 U.S.C. § 271(b) by inducing Exela to submit ANDA No. 78-590 under the Federal Food Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' proposed generic Brimonidine Tartrate Ophthalmic Solution 0.15% product will constitute an act of infringement of the '834 patent;

g. That an order be issued under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of Exela's ANDA No. 78-590 shall be a date which is not earlier than the date of expiration of the '834 patent;

h. That an injunction be issued under 35 U.S.C. § 271(e)(4)(B) permanently enjoining Exela, Paddock, PharmaForce, their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product covered by the '834 patent;

i. That damages or other monetary relief be awarded to Allergan under 35 U.S.C. § 271(e)(4)(C) as appropriate;

j. That a declaration be issued under 28 U.S.C. § 2201 that if Exela, Paddock, PharmaForce, their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf engage in the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' Brimonidine Tartrate Ophthalmic Solution 0.15% product, it will constitute an act of infringement of the '834 patent;

k. That this is an exceptional case under 35 U.S.C. § 285, and that Allergan be awarded reasonable attorneys' fees and costs; and

l. That this Court award such other and further relief as it may deem just and proper.

Demand for Jury Trial

Allergan demands a trial by jury on all issues appropriately tried to a jury.

Dated: April 26, 2007

FISH & RICHARDSON P.C.

By: _____
Jonathan E. Singer

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10730927.doc

PROOF OF SERVICE

I am employed in the County of San Diego. My business address is Fish & Richardson P.C., 12390 El Camino Real, San Diego, California 92130. I am over the age of 18 and not a party to the foregoing action.

I am readily familiar with the business practice at my place of business for collection and processing of correspondence for personal delivery, for mailing with United States Postal Service, for facsimile, and for overnight delivery by Federal Express, Express Mail, or other overnight service.

On April 26, 2007, I caused a copy of the following document(s):

AMENDED COMPLAINT FOR PATENT INFRINGEMENT – JURY TRIAL DEMANDED

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Nancy P. Johnson

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Olejnik et al.

(10) **Patent No.: US 6,641,834 B2**
(45) **Date of Patent: *Nov. 4, 2003**

(54) **COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 18 days.

This patent is subject to a terminal disclaimer.

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(60) Provisional application No. 60/218,200, filed on Jul. 14, 2002.

(51) **Int. Cl.**[7] **A61K 33/14**; A61K 9/00; A61K 9/08

(52) **U.S. Cl.** **424/427**; 424/400; 424/401; 424/466; 424/422; 514/772.4; 514/772.6; 514/249

(58) **Field of Search** 424/661, 400, 424/427, 401, 422; 514/772.4, 772.6, 249

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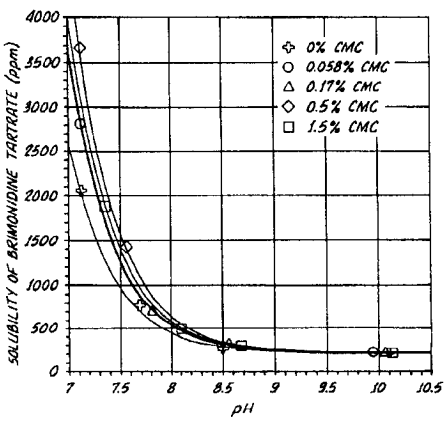
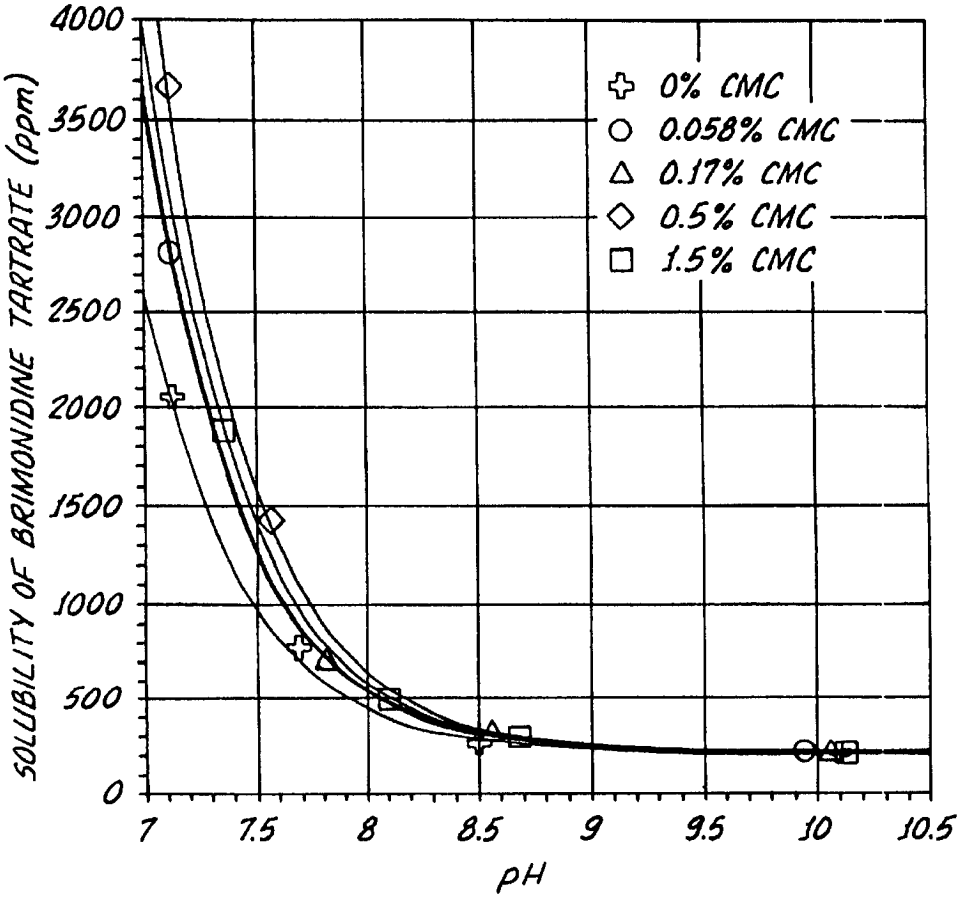
(57) **ABSTRACT**

Compositions useful for improving effectiveness of alpha-2-adrenergic agonist components include carrier components, alpha-2-adrenergic agonist components, solubility enhancing components which aid in solubilizing the alpha-2-adrenergic agonist components. In one embodiment, the alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. In another embodiment, the solubility enhancing components include carboxymethylcellulose.

22 Claims, 1 Drawing Sheet




SOLUBILITY OF BRIMONIDINE TARTRATE (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0
7
7.5
8
8.5
9
9.5
10
10.5
pH
0% CMC
0.058% CMC
0.17% CMC
0.5% CMC
1.5% CMC

COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of application Ser. No. 09/904,018, filed Jul. 10, 2001 which, in turn, claims the benefit of U.S. Provisional Application Ser. No. 60/218,200, filed Jul. 14, 2000. The disclosure of each of the above-noted applications is incorporated in its entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to compositions containing alpha-2-adrenergic agonist components. More particularly, the invention relates to such compositions in which the alpha-2-adrenergic agonist components have enhanced solubility at the therapeutically effective concentrations.

Alpha-2-adrenergic agonist components include chemical entities, such as compounds, ions, complexes and the like, which are effective to act on or bind to Alpha-2-adrenergic receptors and provide a therapeutic effect. Alpha-2-adrenergic agonist components means the agonists themselves and any and all precursors thereof, metabolites thereof and combinations thereof. One of the continuing challenges of formulating compositions having alpha-2-adrenergic agonist components is to render such components more effective. For example, alpha-2-adrenergic agonist components in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration.

Additionally, the dispensed or administered alpha-2-adrenergic agonist components should advantageously be soluble in biological systems or environments, for example, for effective or enhanced in vivo diffusion through cell membranes or lipid bilayers. Some alpha-2-adrenergic agonist components with higher pKa's, for example, greater than about 7, tend to diffuse very well through lipid membranes at pH valves near their pka, because in such circumstances they are predominantly unionized in neutral to alkaline biological environments. However, some of these alpha-2-adrenergic agonist components become insoluble at neutral to alkaline biological pH's. Such insolubility may decrease membrane diffusion capabilities, rendering the alpha-2-adrenergic agonist components less effective and/or their therapeutic effects more variable at a given dosage. Furthermore, solubilized alpha-2-adrenergic agonist components provide other benefits, for example, reduced irritation to tissues that interact with alpha-2-adrenergic agonist components.

There continues to be a need for new compositions containing alpha-2-adrenergic agonist components.

SUMMARY OF THE INVENTION

New alpha-2-adrenergic agonist component-containing compositions have been discovered. The present compositions contain certain materials which are effective in at least aiding or assisting in solubilizing the alpha-2-adrenergic agonist components in the compositions, and preferably in environments to which the compositions are administered or introduced, for example, biological environments, such as the human eye. Preferably, solubilization of the alpha-2-adrenergic agonist components in accordance with the present invention facilitates transport of such components across lipid membranes. Also, preferably such solubilization

allows the provision of more reliable and reproducible dosage forms of the drug. In addition, alpha-2-adrenergic agonist component-containing compositions have been discovered which include preservatives which provide substantial advantages, for example, reduced adverse interactions with the alpha-2-adrenergic agonist components and/or with the patients to whom the compositions are administered, while maintaining preservative effectiveness.

The present compositions preferably enhance the effectiveness of alpha-2-adrenergic agonist components by increasing the apparent water solubility of the alpha-2-adrenergic agonist components, preferably at pH's higher than neutral. The present compositions include, in addition to the adrenergic agonist components, solubility enhancing components (SECs) in amounts effective to enhance the solubility of the alpha-2-adrenergic agonist components. Preferably, the alpha-2-adrenergic agonist components are more soluble in the present compositions having, for example, pH's of about 7 or greater, relative to similar compositions without the SECs. In another embodiment, the alpha-2-adrenergic agonist components of the present compositions are more soluble in neutral, preferably alkaline, biological environments into which the compositions are administered relative to alpha-2-adrenergic agonist components in similar compositions without the SECs.

In one embodiment, the alpha-2-adrenergic agonist components include imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. Preferably, the alpha-2-adrenergic agonist components include quinoxaline components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and biologically compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is referred to as "Brimonidine tartrate."

In a preferred embodiment, the alpha-2-adrenergic agonist components, such as those listed above, are specific for the alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and/or alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonist components are unionized in the compositions. Preferably, the alpha-2-adrenergic agonist components are also unionized in the biological environment into which the compositions are administered.

In a useful embodiment, the SEC includes a polyanionic component. As used herein, the term "polyanionic component" refers to a chemical entity, for example, an ionically charged species, such as an ionically charged polymeric material, which includes more than one discrete anionic charge, that is multiple discrete anionic charges. Preferably, the polyanionic component is selected from polymeric materials having multiple anionic charges, and mixtures thereof.

Particularly useful polyanionic components are selected from anionic polymers derived from acrylic acid (meaning to include polymers from acrylic acid, acrylates and the like and mixtures thereof), anionic polymers derived from methacrylic acid (meaning to include polymers from methacrylic acid, methacrylates, and the like and mixtures thereof), anionic polymers derived from alginic acid (meaning to

include alginic acid, alginates, and the like and mixtures thereof), anionic polymers of amino acids (meaning to include polymers of amino acids, amino acid salts, and the like and mixtures thereof), and the like, and mixtures thereof. Very useful polyanionic components are those selected from anionic cellulose derivatives and mixtures thereof, especially carboxymethylcelluloses.

The polyanionic component preferably is sufficiently anionic to interact with or otherwise affect, in particular increase, the solubility of the alpha-2-adrenergic components. This interaction preferably is sufficient to render the alpha-2-adrenergic components substantially completely soluble at therapeutically effective concentrations. The amount of SEC in the composition preferably is in the range of about 0.1% (w/v) to about 30% (w/v), more preferably about 0.2% (w/v) to about 10% (w/v), and even more preferably about 0.2% (w/v) to about 0.6% (w/v).

The compositions include carrier components, for example, aqueous liquid carrier components. In one embodiment, the compositions have pH's of about 7 or greater, preferably about 7 to about 9, and are ophthalmically acceptable.

In a preferred embodiment, a composition is provided which includes an alpha-2-adrenergic agonist component in an amount effective to provide at least one therapeutic benefit to a patient to whom the composition is administered, an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component and an aqueous liquid carrier component. The alpha-2-adrenergic agonist component preferably comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. The anionic cellulose derivative preferably comprises a carboxymethylcellulose. The concentration of the anionic cellulose derivative in the composition should be about 0.2% (w/v) to about 0.6% (w/v).

In a preferred embodiment, the present compositions are ophthalmically acceptable, e.g. the compositions do not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered.

In one broad aspect of the invention, complexes are formed in the compositions. In one embodiment, the complexes include monomer units derived from at least one quinoxaline component. In a preferred embodiment, the complexes of the present invention are dimers. In a particularly preferred embodiment, the complexes are complexes, especially dimers, of Bromodidine tartrate.

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component and a preservative component in an effective amount to at least aid in preserving the compositions. Preferably, the preservative components include oxychloro components, such as compounds, ions, complexes and the like which are biologically acceptable, chemically stable and do not substantially or significantly detrimentally affect the an alpha-2-adrenergic agonist component in the compositions or the patients to whom the compositions are administered. Such compositions preferably are substantially free of cyclodextrins in the compositions or the patients to whom the compositions are administered.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art.

Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a graph of soluble Brimonidine tartrate verses pH at various carboxymethylcellulose concentrations.

DETAILED DESCRIPTION OF THE INVENTION

Compositions comprising alpha-2-adrenergic agonist components and SECs are provided. The alpha-2-adrenergic agonist components in the present compositions are made more soluble and may be more effectively utilized as therapeutic agents. The SECs employed in the present compositions may be effective in the solubilization of ionized alpha-2-adrenergic agonist components, unionized alpha-2-adrenergic agonist components or both. The present compositions include liquid carrier components and have the characteristics of liquid, for example, aqueous liquid, solutions.

Preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's greater than 7, as compared to identical alpha-2-adrenergic agonist components, at comparable concentrations, in similar compositions without the SECs. More preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's in the range of about 7 to about 10 and, as compared to identical alpha-2-adrenergic agonist components in similar compositions, at comparable concentrations, without the SECs.

Without wishing to be limited by any theory or mechanism of operation, it is believed that solubilized alpha-2-adrenergic agonist components are better able to cross the lipid membranes relative to unsolubilized alpha-2-adrenergic agonist components. It is further believed that the solubilized alpha-2-adrenergic agonist components are physically smaller and are therefore more able to physically permeate or diffuse through the lipid membranes.

In one embodiment, the SECs of this invention are capable of solubilizing the alpha-2-adrenergic agonist components in the biological environments into which they are introduced at therapeutically effective concentrations. Preferably, the biological environments into which the present compositions are introduced have pH's ranging from about 7 to about 9. For example, a composition comprising a SEC and an alpha-2-adrenergic agonist component may be administered to the cornea of an eye, which has a pH of about 7, wherein the alpha-2-adrenergic agonist component is substantially solubilized at the administered area. Furthermore, in one embodiment, the alpha-2-adrenergic agonist components solubilized by SECs at the administered area diffuse through biological lipid membranes more readily than alpha-2-adrenergic agonist components which are not solubilized by SECs. The solubilization of alpha-2-adrenergic agonist components preferably reduces irritation to sensitive tissues in contact or interacting with the alpha-2-adrenergic agonist components.

The presently useful alpha-2-adrenergic agonist components preferably are chosen to benefit from the presence of the SECs. In general, the alpha-2-adrenergic agonist components are provided with increased apparent solubility, preferably increased apparent water solubility, by the presence of the SECs.

Examples of alpha-2-adrenergic agonist components include molecules containing amines. Preferably, the alpha-

2-adrenergic agonist components are amine-containing molecules with pKa's of greater than about 7, more preferably about 7 to about 9.

Alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. As used herein, the term alpha-2 adrenergic agonist includes chemical entities, such as compounds, ions, complexes and the like, that produce a net sympatholytic response, resulting in increased accommodation, for example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or for example, to postsynaptic alpha-2 receptors on smooth muscle cells. A sympatholytic response is characterized by the inhibition, diminishment, or prevention of the effects of impulses conveyed by the sympathetic nervous system. The alpha-2 adrenergic agonists of the invention bind to the alpha-2 adrenergic receptors presynaptically, causing negative feedback to decrease the release of neuronal norepinephrine. Additionally, they also work on alpha-2 adrenergic receptors postsynaptically, inhibiting beta-adrenergic receptor-stimulated formation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2 adrenergic receptors on other intracellular pathways. Activity at either pre- or postsynaptic alpha-2 adrenergic receptors will result in a decreased adrenergic influence. Decreased adrenergic influence results in increased contraction resulting from cholinergic innervations. Alpha-2 adrenergic agonists also include compounds that have neuroprotective activity. For example, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is an alpha-2-adrenergic agonist which has a neuroprotective activity through an unknown mechanism.

Without limiting the invention to the specific groups and compounds listed, the following is a list of representative alpha-2 adrenergic agonists useful in this invention: imino-imidazolines, including clonidine, apraclonidine; imidazolines, including naphazoline, xymetazoline, tetrahydrozoline, and tramazoline; imidazoles, including detomidine, medetomidine, and dexmedetomidine; azepines, including B-HT 920 (6-allyl-2-amino-5,6,7,8 tetrahydro-4H-thiazolo[4,5-d]-azepine and B-HT 933; thiazines, including xylazine; oxazolines, including rilmenidine; guanidines, including guanabenz and guanfacine; catecholamines; and the like and derivatives thereof.

Particularly useful alpha-2-adrenergic agonists include quinoxaline components. In one embodiment, the quinoxaline components include quinoxaline, derivatives thereof and mixtures thereof. Preferably, the derivatives of quinoxaline include (2-imidozolin-2-ylamino) quinoxaline. More preferably, the derivatives of quinoxaline include 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline. The "halide" of the 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline may be a fluorine, a chlorine, an iodine, or preferably, a bromine, to form 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Even more preferably, the derivatives of quinoxaline to be used in accordance with this invention include a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, or Brimonidine tartrate.

Other useful quinoxaline derivatives are well known. For example, useful derivatives of a quinoxaline include the ones disclose by Burke et al U.S. Pat. No. 5,703,077. See also Danielwicz et al 3,890,319. Each of the disclosures of Burke et al and Danielwicz et al is incorporated in its entirety by reference herein.

The quinoxaline and derivatives thereof, for example Brimonidine tartrate, are amine-containing and preferably have pKa's of greater than 7, preferably about 7.5 to 9.

Analogs of the foregoing compounds that function as alpha-2 adrenergic agonists also are specifically intended to be embraced by the invention.

Preferably, the alpha-2-adrenergic agonists, for example the ones listed above, are effective toward activating alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonists, for example Brimonidine tartrate, are substantially unionized in the compositions. In another embodiment, the adrenergic compounds are substantially unionized in the environment to which they are administered, for example the cornea. Without wishing to be limited by any theory or mechanism of action, it is believed that the unionized forms of the adrenergic compounds facilitate their permeation across membrane lipid bilayers.

Any suitable SEC may be employed in accordance with the present invention. In one embodiment, the SECs include pyrrolinidone components. Examples of pyrrolinidone components are polyvinylpyrrolinidones and derivatives thereof. In a preferred embodiment, the SECs include polyanionic components. The useful polyanionic components include, but are not limited to, those materials which are effective in increasing the apparent solubility, preferably water solubility, of poorly soluble alpha-2-adrenergic agonist components and/or enhance the stability of the alpha-2-adrenergic agonist components and/or reduce unwanted side effects of the alpha-2-adrenergic agonist components. Furthermore, the polyanionic component is preferably ophthalmically acceptable at the concentrations used. Additionally, the polyanionic component preferably includes three (3) or more anionic (or negative) charges. In the event that the polyanionic component is a polymeric material, it is preferred that each of the repeating units of the polymeric material include a discrete anionic charge. Particularly useful anionic components are those which are water soluble, for example, soluble at the concentrations used in the presently useful liquid aqueous media, such as a liquid aqueous medium containing the alpha-2-adrenergic components.

The polyanionic component is preferably sufficiently anionic to interact with the alpha-2-adrenergic agonist component. Such interaction is believed to be desirable to solubilize the alpha-2-adrenergic agonist component and/or to maintain such alpha-2-adrenergic agonist component soluble in the carrier component, for example a liquid medium.

Polyanionic components also include one or more polymeric materials having multiple anionic charges.

Examples include:

- metal carboxymethylstarchs
- metal carboxymethylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - metal acrylates and methacrylates
  - alginic acid
  - metal alginates
  - vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - p-styrenesulfonic acid

metal p-styrenesulfonate
2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

In another embodiment, the polyanionic components include anionic polysaccharides which tend to exist in ionized forms at higher pH's, for example, pH's of about 7 or higher. The following are some examples of anionic polysaccharides which may be employed in accordance with this invention.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose.

Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks.

Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of which can be sulfated or nonsulfated, joined by alternating 1-3 and beta 1-4 glycosidic linkages. Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss.

Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water.

Other anionic polysaccharides found useful in the present invention are hydrophilic colloidal materials and include the natural gums such as gellan gum, alginate gums, i.e., the ammonium and alkali metal salts of alginic acid and mixtures thereof. In addition, chitosan, which is the common name for deacetylated chitin is useful. Chitin is a natural product comprising poly-(N-acetyl-D-glucosamine). Gellan gum is produced from the fermentation of pseudomonas elodea to yield an extracellular heteropolysaccharide. The alginates and chitosan are available as dry powders from Protan, Inc., Commack, N.Y. Gellan gum is available from the Kelco Division of Merk & Co., Inc., San Diego, Calif.

Generally, the alginates can be any of the water-soluble alginates including the alkali metal alginates, such as sodium, potassium, lithium, rubidium and cesium salts of alginic acid, as well as the ammonium salt, and the soluble alginates of an organic base such as mono-, di-, or triethanolamine alginates, aniline alginates, and the like. Generally, about 0.2% to about 1% by weight and, preferably, about 0.5% to about 3.0% by weight of gellan, alginate or chitosan ionic polysaccharides, based upon the total weight of the composition, are used to obtain the gel compositions of the invention.

Preferably, the anionic polysaccharides are cyclized. More preferably, the cyclized anionic polysaccharides include less than ten monomer units. Even more preferably, the cyclized polysaccharides include less than six monomer units.

In one embodiment, a particularly useful group of cyclized anionic polysaccharides includes the cyclodextrins. Examples of the cyclodextrin group include, but are not limited to: α-cyclodextrin, derivatives of α-cyclodextrin, β-cyclodextrin, derivatives of β-cyclodextrin, γ-cyclodextrin, derivatives of γ-cyclodextrin, carboxymethyl-β-cyclodextrin, carboxymethyl-ethyl-β-cyclodextrin, diethyl-β-cyclodextrin. dimethyl-β-cyclodextrin, methyl-β-cyclodextrin, random methyl-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and the like and mixtures thereof. Sulfobutylether-β-cyclodextrin is a preferred cyclized anionic polyasaccharide in accordance with the present invention. It is advantageous that the SEC's, including the above mentioned cyclodextrins, employed in this invention be, at the concentration employed, non-toxic to the mammal, human, to inhibit the present incorporation is administered. As used herein, the term "derivatives" as it relates to a cyclodextrin means any substituted or otherwise modified compound which has the characteristic chemical structure of a cyclodextrin sufficiently to function as a cyclodextrin component, for example, to enhance the solubility and/or stability of active components and/or reduce unwanted side effects of the active components and/or to form inclusive complexes with active components, as described herein.

Although cyclodextrins and/or their derivatives may be employed as SECs, one embodiment of the invention may include SECs other than cyclodextrins and/or their derivatives.

A particularly useful and preferred class of polyanionic component includes anionic cellulose derivatives. Anionic cellulose derivatives include metal carboxymethylcelluloses, metal carboxymethylhydroxyethylcelluloses and hydroxypropylmethylcelluloses and derivatives thereof.

The present polyanionic components often can exist in the unionized state, for example, in the solid state, in combination with a companion or counter ion, in particular a plurality of discrete cations equal in number to the number of discrete anionic charges so that the unionized polyanionic component is electrically neutral. For example, the present unionized polyanionic components may be present in the acid form and/or in combination with one or more metals. Since the polyanionic components are preferably ophthalmically acceptable, it is preferred that the metal associated with the unionized polyanionic component be ophthalmically acceptable in the concentrations used. Particularly useful metals include the alkali metals, for example, sodium and potassium, the alkaline earth metals, for example, calcium and magnesium, and mixtures thereof. Sodium is very useful to provide the counter ion in the unionized polyanionic component. Polyanionic components which, in the unionized states, are combined with cations other than H^+ and metal cations can be employed in the present invention.

The amount of SEC in the present compositions is not of critical importance so long as solubility at the alpha-2-adrenergic agonist component is at least somewhat increased and is present in a biologically acceptable amount. Such amount should be effective to perform the desired function or functions in the present composition and/or after administration to the human or animal. In one embodiment, the amount of SEC, preferably the polyanionic component, is sufficient to complex at least in a major amount, and more preferably substantially all, of the alpha-2-adrenergic agonist component in the present composition. In one useful embodiment, the amount of polyanionic component in the present composition is in the range of about 0.1% to about 30% (w/v) or more of the composition. Preferably, the amount of polyanionic component is in the range of about 0.2% (w/v) to about 10% (w/v). More preferably, the amount of polyanionic component is in the range of about 0.2%

(w/v) to about 0.6% (w/v). Even more preferably, the polyanionic component is carboxymethylcellulose and is present in the composition in the range of about 0.2% (w/v) to about 0.6% (w/v). A particularly useful concentration of carboxymethylcellulose in the present compositions is about 0.5%.

In one embodiment, the SECs, for example a carboxymethylcellulose, assist in solubilizing the alpha-2-adrenergic agonist components in the compositions. Although the SECs are capable aiding in the solubilization of ionized alpha-2-adrenergic agonist components, it is preferable that the SECs used in this invention could assist in the solubilization of unionized alpha-2-adrenergic agonist components. For example, in one embodiment, carboxymethylcellulose may help solubilize ionized alpha-2-adrenergic agonist components. In another embodiment, carboxymethylcellulose may help solubilize unionized alpha-2-adrenergic agonist components. In a preferred embodiment, the carboxylmethylcellulose helps solubilize ionized Brimonidine tartrate in the compositions. More preferably, the carboxylmethylcellulose helps solubilize unionized Brimonidine tartrate in the compositions.

In one embodiment, the compositions may also include preservative components or components which assist in the preservation of the composition. The preservative components selected so as to be effective and efficacious as preservatives in the present compositions, that is in the presence of polyanionic components, and preferably have reduced toxicity and more preferably substantially no toxicity when the compositions are administered to a human or animal.

Preservatives or components which assist in the preservation of the composition which are commonly used in pharmaceutical compositions are often less effective when used in the presence of solubilizing agents. In certain instances, this reduced preservative efficacy can be compensated for by using increased amounts of the preservative. However, where sensitive or delicate body tissue is involved, this approach may not be available since the preservative itself may cause some adverse reaction or sensitivity in the human or animal, to whom the composition is administered.

Preferably, the present preservative components or components which assist in the preservation of the composition, preferably the alpha-2-adrenergic agonist components therein, are effective in concentrations of less than about 1% (w/v) or about 0.8% (w/v) and may be 500 ppm (w/v) or less, for example, in the range of about 10 ppm(w/v) or less to about 200 ppm(w/v). Preservative components in accordance with the present invention preferably include, but are not limited to, those which form complexes with the polyanionic component to a lesser extent than does benzalkonium chloride.

Very useful examples of the present preservative components include, but are not limited to oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof. Specific examples of oxy-chloro components useful as preservatives in accordance with the present invention include hypochlorite components, for example hypochlorites; chlorate components, for example chlorates; perchlorate components, for example perchlorates; and chlorite components. Examples of chlorite components include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures therefor. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Purite T by Allergan, Inc. Other examples of oxidative preservative components includes peroxy components. For example, trace amounts of peroxy components stabilized with a hydrogen peroxide stabilizer, such as diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid, may be utilized as a preservative for use in components designed to be used in the ocular environment. Also, virtually any peroxy component may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. Examples of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, may not be stabilized utilizing the present system. See, for example, Martin et al U.S. Pat. No. 5,725,887, the disclosure of which is incorporated in its entirety herein by reference.

Preservatives other than oxidative preservative components may be included in the compositions. The choice of preservatives may depend on the route of administration. Preservatives suitable for compositions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic compositions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds and the like known generically as "benzalkonium chloride." For compositions to be administered by inhalation, however, the preferred preservative is chlorbutol and the like. Other preservatives which may be used, especially for compositions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and mixtures thereof, such as the mixture of methyl, ethyl, propyl, butyl esters and the like which is sold under the trade name "Nipastat."

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component, a preservative component in an effective amount to at least aid in preserving, preferably in an amount effective to preserve, the compositions and a liquid carrier component. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which (1) do not substantially or significantly detrimentally affect the alpha-2-adrenergic agonist components in the compositions or the patients to whom the compositions are administered, and (2) are substantially biologically acceptable and chemically stable. Such compositions in accordance with the present invention comprise an alpha-2-adrenergic agonist component, an oxy-chloro component, and a liquid carrier component, and preferably are substantially free of cyclodextrins.

The carrier components useful in the present invention are selected to be non-toxic and have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. In one embodiment, the carrier component is a liquid carrier. In a preferred embodiment, the carrier component is a liquid aqueous carrier component. A

particularly useful aqueous liquid carrier component is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution. The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5. The liquid medium preferably has an ophthalmically acceptable tonicity level, for example, of at least about 200 mOsmol/kg, more preferably in the range of about 200 to about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the carrier component substantially corresponds to the tonicity of the fluids of the eye, in particular the human eye.

In one embodiment, the carrier components containing the SECs and the alpha-2-adrenergic agonist components may have viscosities of more than about 0.01 centipoise (cps) at 25° C., preferably more than about 1 cps at 25° C., even more preferably more than about 10 cps at 25° C. In a preferred embodiment, the composition has a viscosity of about 50 cps at 25° C. and comprises a conventional buffer saline solution, a carboxymethylcellulose and a Brimonidine tartrate.

In order to insure that the pH of the aqueous liquid carrier component, and thus the pH of the composition, is maintained within the desired range, the aqueous liquid carrier component may include at least one buffer component. Although any suitable buffer component may be employed, it is preferred to select such component so as not to produce a significant amount of chlorine dioxide or evolve significant amounts of gas, such as CO_2. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components are advantageously used in the present invention.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid aqueous carrier component and do not have deleterious or toxic properties which could harm the human or animal to whom the present compositions are administered. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring agents, surface active agents, thickeners, lubricants, and the like, for example, such additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gun tragacanth and gun acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof. Such aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gun tragacanth, naturally-occurring phosphatides, for example, soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

In one broad aspect of the invention, complexes are formed in the present compositions. In one embodiment, the complexes include at least one monomer unit of a quinoxaline component. Examples of quinoxaline components include quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts thereof, esters thereof, other derivatives thereof, and the like and mixtures thereof. For example, in one embodiment, a complex of the present invention may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units. In another embodiment, the complex may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units and Brimonidine tartrate monomer units.

In a preferred embodiment, the complexes of the present invention are dimers. For example, a dimer in accordance with the present invention may include a quinoxaline and a 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. Preferably, a dimer in accordance with the present invention includes two Brimonidine tartrate monomer units.

Without wishing to limit the invention to any theory or mechanism of operation, it is believed that any peroxide forming agent or strong oxidizing agent such as the oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof may facilitate the formation of the complexes, preferably complexes of alpha-2-adrenergic agonist components. For example, dimers of Brimonidine tartrate monomer units are believed to be formed in the presence of chlorites, preferably stabilized chlorine dioxide.

Furthermore, it is believed that the interactions between the monomers which serve to hold the monomers or mono-

mer subunits together to form a complex, preferably an oligomer and more preferably a dimer, may include, but not limited to, covalent bonding, ionic bonding, hydrophobic bonding, electrostatic bonding, hydrogen bonding, other chemical and/or physical interactions, and the like and combinations thereof. Such complexes may disassociate in liquid, for example, aqueous liquid, media. In one embodiment, the monomers or monomer subunits are held together by other than covalent bonding. In one embodiment, the monomers or monomer subunits are held together by electrostatic bonding or forces.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Brimonidine tartrate has a pKa of about 7.78. The pH-solubility profile of 0.5% (w/v) Brimonidine tartrate in a formulation, Ophthalmic Solution, was established in the pH range of about 5 to about 8 at 23° C. Table 1. It will be understood that concentrations of adrenergic agonists other than 0.5% may be used, so long as they have therapeutic activity. Likewise, the temperature may be varied, for example, solubility curves may be performed at 37° C. (98.6° F.). The formulation vehicle was prepared by first dissolving polyvinyl alcohol (PVA) in water. The PVA was added to approximately ⅓ of the required total amount of purified water with constant stirring. The slurry was stirred for 20–30 minutes and then heated to 80–95° C. with constant stirring. The mixture was removed from the heat source within 1 hour after having reached the temperature of 80–90° C. and stirred for an additional 10 minutes to ensure homogeneity (Part I). The other ingredients of the Ophthalmic Solution, except for Brimonidine tartrate, were dissolved in a separate container with an additional ⅓ of the required total amount of purified water (Part II). The PVA mixture (Part I) was then quantitatively transferred to Part II using several rinse volumes of purified water. The solution was adjusted to final volume with purified water without pH adjustment.

Brimonidine tartrate was weighed and transferred to a 10 mL test tube containing 5 mL of the formulation vehicle described above. The pH of each sample was then adjusted to a desired value using dilute sodium hydroxide and/or dilute hydrochloric acid. The samples were placed in a rack on a stir plate and stirred at high speed to achieve uniform mixing for 2 days; a partition was placed between the rack and the stir plate to prevent any heat diffusion from the stir plate to the samples. The temperature of the laboratory was monitored throughout the study and was found to be 23±1° C.

At the end of two days of stirring, the pH value of each sample was measured, and then approximately 1 mL of each sample was placed in a micro centrifuge tube (polypropylene) and centrifuged at 4,000 rpm for 10 minutes. The supernatant was filtered through a 1 μm filter unit (Whatman, 13 mm, PTFE). The first 3–4 drops of the filtrate were discarded; the rest of the filtrate was received and diluted quantitatively with HPLC mobile phase. The dilute sample was then injected directly on the HPLC column (Dupont Zorbax, 250 mm×4.6 mm, 5 μm) for Brimonidine tartrate assay in order to quantify the amount of Brimonidine tartrate. A control of 10.05% Brimonidine tartrate was prepared in the formulation vehicle at pH 6.3–6.5 and assayed before (untreated) and after (treated) centrifugation and filtration. This was done to evaluate the potential loss of Brimonidine tartrate in these two steps of the sample preparation. To ensure reproducibility, the study was repeated on consecutive days.

TABLE I

0.5% Brimonidine tartrate in Ophthalmic Solution.

Ingredient	Percent (w/v)
Brimonidine tartrate	0.50
Benzalkonium Chloride, NF	0.0050
Polyvinyl Alcohol, USP	1.4
Sodium Chloride, USP	0.66
Sodium Citrate, Dihydrate, USP	0.45
Hydrochloric Acid, NF or Sodium Hydroxide, NF for pH adjustment	5–8
Purified Water, USP	QS

The solubility data for Brimonidine tartrate in the formulation vehicles are presented in Table II. The results show that the solubility of Brimonidine tartrate is highly pH-dependent and spans more than two orders of magnitude over the pH range of 5–8. The solubility decreases sharply as the pH increases. The results for the treated and untreated controls are very close, suggesting that centrifugation and filtration does not cause any significant loss of Brimonidine tartrate. The two solubility profiles obtained on consecutive days agree with each other.

TABLE II

Solubility of Brimonidine tartrate in the Ophthalmic Solution Over pH Range of 5 to 8.

	STUDY 1		STUDY 2	
Sample	pH[a]	Solubility[c]	pH[a]	Solubility[c]
1	5.55	≧1644[b]	5.5(	≧200.6[b]
2	5.92	132.6	5.92	160.8
3	6.14	30.4	6.0(	50.1
4	6.57	7.55	6.9(	3.19
5	7.00	2.69	7.4(	1.19
6	7.45	1.17	7.7	0.63
7	7.83	0.62	7.8(	0.58
8	—	—	7.8	0.54
Control / (untreated)	—	0.486[c]	—	—
Control / (treated)	—	0.484[d]	—	—

[a]Measured after stirring for two-days before sample withdrawal for centrifugation and filtration.
[b]Represents theoretical concentration based on sample weight. The sample solution was clear indicating that all of the Brimonidine tartrate had dissolved.
[c]Concentration of Brimonidine tartrate in control before centrifugation and filtration step.
[d]Concentration of Brimonidine tartrate in control after centrifugation and filtration step.
[e]% w/v.

EXAMPLE 2

The pH-solubility profiles of Brimonidine tartrate in compositions (solutions) containing SECs and oxy-chloro components were determined. Particularly, the effects of sodium carboxymethylcellulose (CMC), an SEC, on the solubility of Brimonidine tartrate at various pH conditions were determined. The various concentrations of CMC tested with Brimonidine tartrate were 0%, 0.056%, 0.17%, 0.5%, 1.5% (w/v), Table III.

The samples tested also contained isotonic components, buffer components, and stabilized chlorine dioxide (Purite™), Table III. Sodium carboxymethyl-cellulose, sodium chloride, potassium chloride, calcium chloride

dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

TABLE III

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	
Brimonidine tartrate	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
CMC	0.0%	0.056%	0.17%	0.5%	1.5%	(w/v)
Stabilized chlorine dioxide[a]	0.005%	0.005%	0.005%	0.005%	0.005%	(w/v)
Sodium chloride	0.58%	0.58%	0.58%	0.58%	0.58%	(w/v)
Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)
Calcium chloride, dihydrate	0.02%	0.02%	0.02%	0.02%	0.02%	(w/v)
magnesium chloride, hexahydrate	0.006%	0.006%	0.006%	0.006%	0.006%	(w/v)
boric acid	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
sodium tetraborate, decahydrate	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)

[a]Sold under the trademark Purite ™ by Allergan, Inc.

Each sample (1 through 5) was subjected to a range of pH's from about 7 to about 10. The vials containing the sample solutions were placed on a laboratory rotator and left for equilibration for fifteen days at room temperature (~21° C.). The sample solutions were filtered using a 25 mm diameter polysulfone cellulose acetate syringe type filter with 0.45 μm pore size. The filtered solutions were assayed for Brimonidine.

Conventional HPLC and detection techniques were used to detect and determine the concentrations of soluble Brimonidine tartrate. Table IV. The solubility is plotted against pH for each CMC concentration. The experimental data points were fitted to a modified Henderson-Hasselbalch equation using a nonlinear least squares routine (Deltagraph version 4.0 DeltaPoint, Inc.), FIG. 1. The R^2 values show the goodness of fit between the experimental values and the theoretical equation to be better than 0.991.

TABLE IV

	Solubility of Brimonidine tartrate (%)				
	0% CMC	0.056% CMC	0.17% CMC	0.5% CMC	1.5% CMC
pH					
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
7.56				0.1451	
7.68	0.0786				
7.77		0.0721			
7.81			0.0735		
8.10					0.0498
8.46				0.0313	
8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

FIG. 1 clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.056% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.5%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

EXAMPLE 3

Brimonidine Tartrate Dimers.

Brimonidine tartrate is added to a test tube containing a composition including chlorite. The test tube was allowed to equilibrate for ten days. Samples obtained from the test tube is analyzed. It is observed that a portion of the Brimonidine tartrate monomer units conjugated to form dimers.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

What is claimed is:

1. A therapeutically effective aqueous ophthalmic composition comprising:

up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at about 21° C.

2. The composition of claim **1** which includes up to 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

3. The composition of claim **1** which includes about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.

4. The composition of claim **1** which includes 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

5. The composition of claim **1** having a pH of 7.0 or greater.

6. The composition of claim **1** which further comprises a preservative selected from the group consisting of an oxychloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

7. The composition of claim **6** wherein the oxy-chloro component comprises a chlorite component.

8. The composition of claim **1** which is substantially free of anionic cellulosic derivatives.

9. The composition of claim **1** which is substantially free of carboxymethyl cellulose.

10. A therapeutically effective aqueous ophthalmic composition comprising:

up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the composition at about 21° C.

11. The composition of claim **10** which includes up to 0.15% (w/v) of the component.

12. The composition of claim **10** which includes about 0.15% (w/v) of the component.

13. The composition of claim **10** which includes 0.15% (w/v) of the component.

14. The composition of claim **10** having a pH of 7.0 or greater.

15. The composition of claim **10**, which further comprises an oxy-chloro component in an amount effective to at least assist in preserving the composition.

16. The composition of claim **15** wherein the oxy-chloro component comprises a chlorite component.

17. The composition of claim **10** which is substantially free of anionic cellulosic derivatives.

18. The composition of claim **10** which is substantially free of carboxymethyl cellulose.

19. The composition of claim **6** in which the preservative comprises benzalkonium chloride.

20. The composition of claim **10** which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

21. The composition of claim **20** in which the preservative comprises benzalkonium chloride.

22. The composition of claim **20** in, which the preservative comprises a oxy-chloro component.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

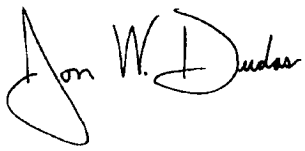
PATENT NO. : 6,641,834 B2
DATED : November 4, 2003
INVENTOR(S) : Olejnik et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10,
Line 10, delete "Purite T" and insert in place thereof -- Purite™ --

Signed and Sealed this

Twentieth Day of January, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,641,834 B2
DATED : November 4, 2003
INVENTOR(S) : Olejnik et al.

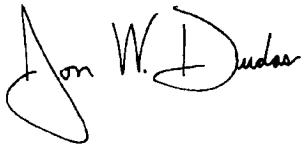
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 3,
Line 48, delete "Bromodidine" and insert in place thereof -- Brimonidine --

Column 5,
Line 61, delete "disclosc" and insert in place thereof -- disclosed --

Signed and Sealed this

Twenty-fourth Day of February, 2004



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Effects of Common Ophthalmic Preservatives on Ocular Health

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ABSTRACT

Preservatives are an important component of ophthalmic preparations, providing antimicrobial activity in the bottle and preventing decomposition of active drug. Often underrecognized, however, are the significant cytotoxic effects of preservatives associated with long-term therapy and especially use of multiple preserved drugs. The most common preservatives in ophthalmic preparations for glaucoma and surface eye disease—benzalkonium chloride (BAK), chlorobutanol, sodium perborate, and stabilized oxychloro complex (SOC)—were reviewed. Compared with other preservatives, SOC caused the least amount of damage to rabbit corneal epithelial cells. BAK has demonstrated cytotoxic effects in cell culture, as well as in animal and human studies. Physicians should consider treatment with new-generation preparations containing low-risk preservatives such as SOC, especially in patients receiving multiple ophthalmic medications.

Keywords: ophthalmic preservatives; benzalkonium chloride; chlorobutanol; SOC; sodium perborate

INTRODUCTION

The contents of multidose medication containers used twice daily often undergo bacterial contamination within 1 or 2 weeks.[1] As a result, the US Food and Drug Administration and the US Pharmacopoeia mandate that all multidose ophthalmic preparations contain a preservative to ensure a nonhazardous degree of contamination. By providing a level of antimicrobial activity in the bottle, preservatives limit bacterial, mycotic, and amoebal ocular infections caused by contaminated solutions and prolong shelf life by preventing biodegradation and maintaining drug potency. The primary concern with many preservatives is not their efficacy but, rather, their recognized cytotoxic side effects.[2]

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High concentrations of some preservatives can damage and irritate ocular tissue. Preservative-free products may prevent the toxic side effects, but they are expensive and the small unit-dose containers can be difficult to use, hindering compliance.[3] Nonetheless, some patients require preservative-free products because of sensitivities or allergies. The goal of the physician should be to prescribe effective agents that contain preservatives with minimal effects on ocular tissues.

CLINICAL RELEVANCE

In chronic diseases, such as glaucoma or dry eye syndrome, high concentrations of preservatives or repeated exposure to preserved medications increases the likelihood of adverse effects. For example, high incidences of endothelial damage, epithelial edema, and bulbous keratopathy characterize patients with glaucoma, dry eyes, infections, or iritis whose use of preservative-containing ophthalmic solutions is frequent and prolonged.[4] Even with infrequent administration, preserved solutions may be contraindicated in the presence of trophic ulcers or other states of severely compromised corneal epithelial integrity.[5] Patients with defective epithelia or corneal ulcers may be most at risk because of increased penetration of the medication and preservatives.[4]

Glaucoma

Long-term use of antiglaucoma drugs has been linked to toxic and inflammatory changes of the ocular surface.[6-8] Conjunctival biopsies from glaucoma patients show a significant increase in immune cells and fibroblasts possibly related to prolonged treatment.[9,10] Repeated doses of preserved eyedrops can have a cumulative effect, and extended contact with the epithelium may lead to chronic irritation and subconjunctival fibrosis, increasing the risk that trabeculectomy will fail.[7,11] Multidrug treatment of glaucoma may also raise the risk for the ocular surface effects of preservatives. Less frequent daily administration, lower preservative concentrations (currently □0.01% for most antiglaucoma drugs), and new formulations may help to minimize this ocular surface damage.

Keratoconjunctivitis sicca (KCS)

Patients with severe KCS may need to instill tear substitutes as often as every 20 minutes. Preservatives may worsen the condition by disrupting the precorneal tear film and damaging the epithelial surface.[5] Many corneal specialists believe that KCS may be aggravated by frequent use of preservative-containing artificial tears, especially because these patients may not produce enough natural tears to dilute a harmful preservative.[2,5] Overuse of nonprescription eyedrops can also contribute to adverse effects. When patients with glaucoma or KCS discontinue use of preservative-containing medications, allergic complaints or chronic irritation of the conjunctiva and eyelids also ceases.[4]

Managing Preservative-Induced Ocular Damage

Damage due to ophthalmic preservatives often goes unnoticed because it is difficult to differentiate side effects of an active ingredient from those of the preservative.

The following sections review the mechanism of action and results of tissue culture and animal studies to compare toxic effects of four preservatives.

COMMONLY USED PRESERVATIVES

A spectrum of preservatives are found in nearly every type of ophthalmic solution. Benzalkonium chloride (BAK) is one of the most commonly used preservatives. Less common are benzododecinium bromide (BDD), cetrimonium chloride, thiomersal, methyl parahydroxybenzoate, sorbic acid, polyquarternium ammonium chloride (PQAC), polyaminopropyl biguanide, and hydrogen peroxide. Tables 1 and 2 list commonly used products and their preservative concentrations.

Table 1. Preservative Composition of Antiglaucoma Medications

Trade Name	Manufacturer	Preservative
Alphagan®	Allergan, Inc.	BAK 0.005%
Alphagan P®	Allergan, Inc.	SOC 50 ppm
Azopt®	Alcon	BAK 0.01%
Betagan®	Allergan, Inc.	BAK 0.005%
Betoptic S®	Alcon	BAK 0.01%
Cosopt®	Merck & Co., Inc.	BAK 0.0075%
Lumigan™	Allergan, Inc.	BAK 0.005%
Propine®	Allergan, Inc.	BAK 0.005%
Rescula®	CIBA Vision	BAK 0.015%
Timoptic®	Merck & Co., Inc.	BAK 0.01%
Timoptic-XE®	Merck & Co., Inc.	BDD 0.012%
Trusopt®	Merck & Co., Inc.	BAK 0.0075%
Xalatan®	Pharmacia & Upjohn	BAK 0.02%

SOC = stabilized oxychloro complex.

Mechanism of Action

Preservatives interfere with microbial organisms by causing lysis of plasma membranes, inhibiting cellular metabolism, oxidizing or coagulating cellular constituents, or promoting hydrolysis.[2] Preservatives can be classified in two main categories as oxidants or detergents.[12] Oxidative preservatives, such as stabilized oxychloro complex (SOC) and sodium perborate, are usually small molecules that penetrate cell membranes and disrupt cellular function by modifying lipids, proteins, and DNA.[13] Their membrane-destabilizing activity is less potent than that of

Table 2. Over-the-Counter Products for Ocular Surface Disease and Their Preservative Concentrations

Product Name	Manufacturer	Preservative	Use
GenTeal®	CIBA Vision	Sodium perborate	Artificial tears
Hypotears®	CIBA Vision	BAK 0.01%	Artificial tears
Naphcon-A®	Alcon	BAK 0.01%	Vasoconstrictor
Refresh Tears®	Allergan, Inc.	SOC 50 ppm	Artificial tears
Tears Naturale II®	Alcon	Polyquad 0.001%	Artificial tears
Vasocon-A®	CIBA Vision	BAK 0.01%	Vasoconstrictor
Visine®	Pfizer	BAK 0.01%	Vasoconstrictor

detergent preservatives. At low levels, oxidative preservatives have an advantage over detergent preservatives by providing enough activity against microorganisms while exerting only negligible toxic effects on eukaryotic cells. This occurs because many microorganisms cannot cope with oxidative stress. In comparison, mammalian cells are equipped with antioxidants, oxidases, and catalases to neutralize the effect of a low-level oxidant.

Detergent preservatives, such as BAK, are usually monomeric or polymeric compounds that have surfactant effects and alter cell membrane permeability by causing lipid dispersion and lysis of cytoplasmic contents.[14] Some may have a similar action on eukaryotic cells and cause cytotoxic effects. Mammalian cells cannot neutralize detergent preservatives, which can be incorporated into the cell by liposomes or other intracellular vacuoles and cause cellular damage.[15]

Purite®* (SOC)

SOC destroys many types of bacteria as well as the fungus *Aspergillus niger*.[16] Introduced in 1996, it consists of an equilibrium mixture of oxychloro species—99.5% chlorite (ClO_2), 0.5% chlorate (ClO_3), and trace amounts of chlorine dioxide (ClO_2)—that have bactericidal and viricidal activity.[17] In saline solution, SOC generates chlorine dioxide free radicals in the presence of microbial contamination. However, SOC is an oxidizing, not a chlorinating, agent.[12] The free radicals provide the antimicrobial activity by oxidizing unsaturated lipids and glutathione in the cell.[12] When SOC is administered in the eye, it is converted into natural tear components, such as sodium and chloride ions, oxygen, and water. This conversion occurs by way of cascade-type reactions between SOC and tear-film components and photolytic reactions between SOC and light.[16,17]

Mild cytotoxic effects and an excellent safety record have earned SOC a US Environmental Protection Agency category II rating as a mild eye irritant on the basis of rabbit studies. Although exposure to 2% SOC can produce slight irritation of

*Registered trademark of Allergan, Inc., Irvine, Calif, USA.

the conjunctiva, cornea, and eyelid, this concentration is higher than that used in most commercial products. Efficacy at low concentrations (0.005% w/v) that are benign to the eye makes SOC an ideal ophthalmic preservative. Safety and tolerability were established in a study of 62 patients with mild to moderate dry eye who were treated with an SOC-containing product four to eight times per day for 4 weeks.[18] No evidence of in vivo or in vitro mutagenicity or carcinogenicity has been found.

Chlorine dioxide has been used since 1944 to purify water, and conventional doses appear to be safe for that indication.[17] Mild cytotoxic effects make it a common ingredient in toothpaste, mouthwash, and antacids. Chlorine dioxide destroys microorganisms in fish, fruit, and vegetables without altering the food's nutritive and organoleptic qualities.[17]

Sodium Perborate

One of the first oxidative preservatives, sodium perborate is converted to hydrogen peroxide when combined with water. Sodium perborate oxidizes cell walls or membranes, affects membrane-bound enzymes, and disrupts protein synthesis. On entering the eye, it is rapidly decomposed to water and oxygen by catalase and other enzymes in the conjunctival sac.[16] Sodium perborate is bactericidal and can kill *A. niger*.[16] Low levels retain antimicrobial activity and are comfortable in the eye. However, hydrogen peroxide levels between 30 and 100 ppm, normally produced by ophthalmic preparations containing sodium perborate, can cause ocular stinging.[19,20] Limited testing has also identified sodium perborate as a direct-acting in vitro mutagen.[21] It can also destabilize cell walls and membranes, albeit to a lesser degree than other types of preservatives.

BAK

The quaternary ammonium compound BAK is the most common antimicrobial preservative,[3,5] found at an average concentration of 0.01% (range, 0.004%–0.02%)[3] in topical multiuse ophthalmic preparations. Nearly all antiglaucoma medications contain BAK. Highly efficacious against numerous microbes, BAK denatures proteins and causes lysis of cytoplasmic membranes. The surfactant effect of quaternary ammonium compounds, including BAK, can solubilize the intercellular cement of the corneal epithelium, thereby increasing the compound's penetration.[4,14] Moreover, because BAK can accumulate and remain in ocular tissue for relatively lengthy periods,[4,15] it can induce different types of cell death in a dose-dependent manner: growth arrest at low concentrations, apoptosis at 0.01%, and necrosis at higher concentrations.[21]

In an antiglaucoma preparation, BAK does not alter the drug's ability to lower intraocular pressure but can modify the ocular surface with long-term use.[22] For example, timolol maleate, which contains 0.01% BAK, rapidly decreased cell viability and numbers in a human conjunctival cell line.[23] Similarly, patients treated with timolol maleate 0.5% containing 0.01 g/100 mL of BAK exhibited ocular surface damage attributed to a reduced rate of aqueous layer production and impairment of the tear-film mucus layer.[24] In another study, 127 patients instilling various antiglaucoma drugs containing BAK had significant conjunctival metaplasia compared with patients not using topical treatment.[25] There was no significant difference on cytologic examination between those using any of the medications for less or more than

1 year, suggesting that the damage occurred relatively quickly. Long-term use of antiglaucoma medications containing BAK changes the conjunctival surface and tear-film function,[26] which may increase the risks attendant on future glaucoma surgery.

Patients with dry eye syndrome may have increased vulnerability to BAK-induced effects. Artificial tears containing BAK enhance corneal epithelial permeability, contributing to ocular surface disease.[27] In these patients, the cornea is particularly susceptible to the effects of preservatives because the epithelium is exposed to the full strength of topical preparations.[2] Further, severely affected patients do not produce enough tears to dilute the compound in the eyedrop. Ophthalmic preparations that contain high concentrations of BAK interfere with the integrity of the superficial lipid layer and reduce tear breakup time, causing the duplex tear film to become unstable.[28,29] This compromised stability may not be physiologically harmful, as the lipid layer of the tear film is re-formed every 15 to 30 seconds, but should be taken into account for patients with a compromised tear film.[28] Ideally, these individuals should use products with preservatives that do not break up the tear film. At low BAK concentrations or with infrequent use, BAK-preserved preparations may pose little risk.

Chlorobutanol

As an alcohol-based preservative, chlorobutanol lacks surfactant activity[14]; therefore, unlike BAK, it does not increase penetration of additional chlorobutanol molecules into the cell.[4] Instead, chlorobutanol disorganizes the lipid structure of the membrane, which increases permeability and leads to cell lysis. Chlorobutanol has broad-spectrum antimicrobial action. In vivo, even at concentrations 100 times that of commercial products, it did not damage rabbit cornea, including the endothelium.[4] Chlorobutanol 0.5% did not affect the stability of the tear-film lipid layer in non–contact lens users[30] and enhanced in vitro transcorneal permeation of ibuprofen.[31]

Despite its relative safety, chlorobutanol 0.5% m/v in artificial tears caused irritation in more than 50% of patients in a double-blind crossover study,[32] most likely as a result of cellular retraction and cessation of normal cytokinesis, cell movement, and mitotic activity.[33] Degeneration of human corneal epithelial cells and generation of conspicuous membranous blebs have also been observed.[34] In normal intact rabbit corneas, chlorobutanol 0.5% caused cytoplasmic swelling and occasional breaks in the external cell membrane. In keratectomized rabbit corneas, some mitochondria showed swollen and distorted cristae.[35] A 0.1% concentration caused near-complete loss of the squamous cell layer in isolated rabbit cornea, suggesting disruption of the barrier and transport properties of the corneal epithelium.[35] Chlorobutanol also inhibits oxygen use by the cornea, which increases susceptibility to infection.[36]

Another study,[37] however, found minimal cytotoxic effects of chlorobutanol 0.5% in artificial tears given twice a day for 12 days to pigmented rabbits. Scanning electron microscopy of the corneal epithelial surface detected only occasional cell exfoliation, which peaked after 2 to 3 days and returned close to zero at day 12.[37] Also, compared with BAK 0.004% to 0.02%, chlorobutanol 0.2% to 0.5% is less toxic to rabbit corneal epithelial cells in vitro.[38] In human corneal epithelial cells, the cytotoxic effects of chlorobutanol occur less rapidly and are less severe than those of BAK.[33]

SOC Compared With Other Preservatives

Relative to other preservatives, SOC is minimally toxic to the eye, as determined by scanning electron microscopy. In one study,[39] rabbits were treated four times a day for 7 days with artificial tears containing polyquad 0.001%, sodium perborate, or SOC 50 ppm. On completion of the study, the corneas were removed, fixed in 2.6% glutaraldehyde, osmicated, serially dehydrated, and critical point dried. The specimens were mounted on aluminum stubs, gold sputtered-coated, and evaluated. The untreated rabbit corneal epithelium had extensive microvilli and tight intercellular junctions (Fig 1), as did the eye treated with SOC (Fig 2), and was nearly identical to the eye treated with sodium perborate (Fig 3). The eye exposed to polyquad 0.001% showed extensive superficial epithelial erosion and lack of protruding microvilli (Fig 4). Compared with the untreated eye, the extent of corneal epithelial damage was polyquad > sodium perborate > SOC.[38]

Attempts to improve drug tolerability by minimizing the toxic effects of preservatives are underway. One aim is to decrease cumulative exposure to the preservative. A once-daily form of timolol with 0.012% BDD (a preservative similar to BAK) is available; however, BDD also damages the corneal epithelium and the gel-forming preparation may prolong contact of the preservative with the corneal surface.[3] Another approach is to reformulate existing products with better-tolerated preservatives. One such product, a brimonidine compound approved by the FDA in March 2001, has replaced BAK with SOC in the current formulation. A 12-month clinical comparison in patients with glaucoma or ocular hypertension[40] showed that brimonidine-SOC was well tolerated and produced a significantly lower incidence of allergic conjunctivitis than brimonidine, as well as equivalent IOP-lowering efficacy.

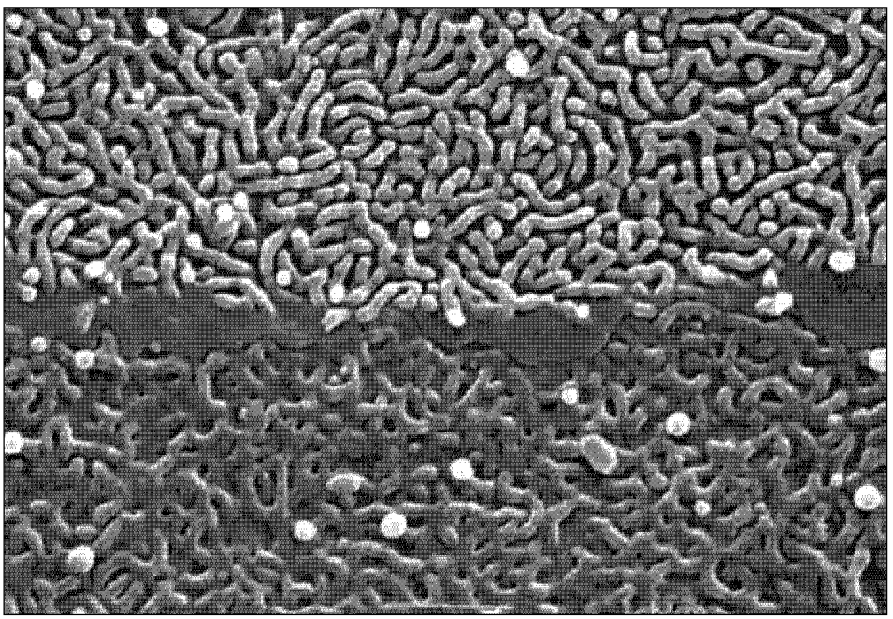

Fig 1. Scanning electron microscopy of untreated rabbit corneal epithelium. The tissue is normal, with extensive microvilli and tight intercellular junctions (□14,000).

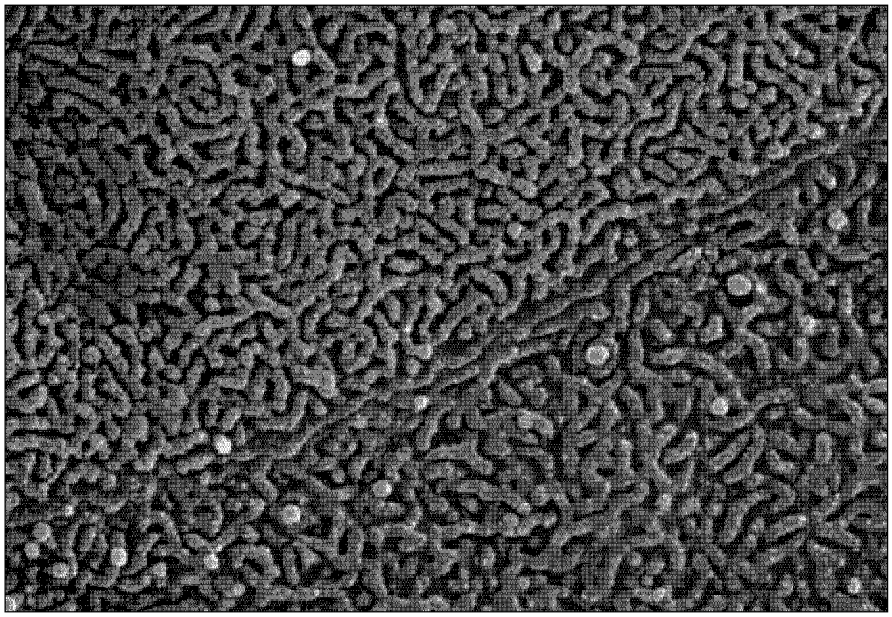

Fig 2. Scanning electron microscopy of rabbit corneal epithelium treated with SOC. The epithelium is normal with extensive microvilli and tight intercellular cell-to-cell junctions (□14,000).

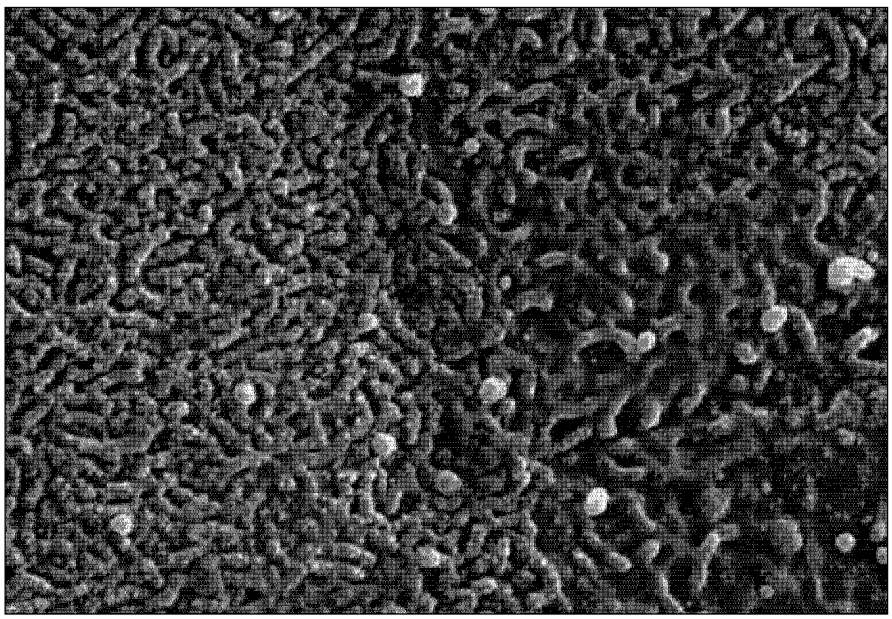

Fig 3. Scanning electron microscopy of rabbit corneal epithelium treated with sodium perborate. The mostly normal epithelium has extensive microvilli and tight epithelial cell-to-cell junctions (□14,000).

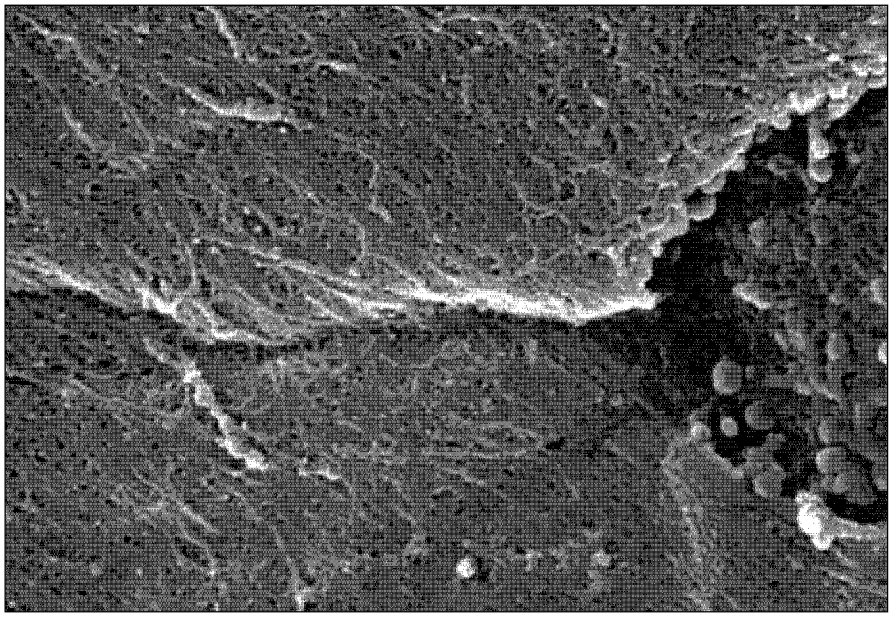

Fig 4. Scanning electron microscopy of rabbit corneal epithelium treated with polyquad 0.001%. Extensive superficial epithelial erosion and lack of protruding microvilli are evident (□14,000).

CONCLUSIONS

Many preservatives in eyedrops induce histopathologic, inflammatory, and toxic changes on the ocular surface. Choosing eyedrops with a less harmful preservative or with lower concentrations of preservatives can be beneficial to the patient. SOC represents a new generation of ophthalmic preservative that breaks down into natural tear components on instillation and thus has low potential to cause toxic effects. Preservative-induced toxic reactions can escalate with the use of multiple ophthalmic drops. Therefore, physicians should consider drugs containing low-risk preservatives or preservatives at concentrations least likely to cause damage.

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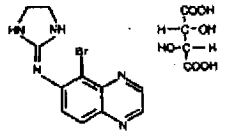
0849

PACIFIC PHARMA.

BRIMONIDINE TARTRATE
ophthalmic solution, 0.2%
sterile

DESCRIPTION

Brimonidine tartrate ophthalmic solution 0.2% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It has a molecular weight of 442.24 as the tartrate salt and is soluble in water (5.6 mg/mL) at pH 6.5. The structural formula is:



Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number 59803-98-4

In solution, Brimonidine tartrate ophthalmic solution 0.2% has a clear, greenish-yellow color. It has an osmolality of 280 - 330 mOsm/kg and a pH of 5.6 - 6.6

Each mL of Brimonidine tartrate ophthalmic solution contains: **Active ingredient:** brimonidine tartrate 0.2% (2 mg/mL). **Preservative:** benzalkonium chloride (0.05 mg). **Inactives:** citric acid; polyvinyl alcohol; sodium chloride; sodium citrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of action: Brimonidine tartrate ophthalmic solution is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacokinetics: After ocular administration of a 0.2% solution, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

Clinical Evaluations: Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

In comparative clinical studies with timolol 0.5%, lasting up to one year, the IOP lowering effect of Brimonidine tartrate ophthalmic solution was approximately 4-6 mm Hg compared with approximately 6 mm Hg for timolol. In these studies, both patient groups were dosed BID; however, due to the duration of action of Brimonidine tartrate ophthalmic solution, it is recommended that Brimonidine tartrate ophthalmic solution be dosed TID. Eight percent of subjects were discontinued from studies due to inadequately controlled intraocular pressure, which in 30% of these patients occurred during the first month of therapy. Approximately 20% were discontinued due to adverse experiences.

INDICATIONS AND USAGE

Brimonidine tartrate ophthalmic solution is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The IOP lowering efficacy of Brimonidine tartrate ophthalmic solution diminishes over time in some patients. This loss of effect appears with a variable time of onset in each patient and should be closely monitored.

CONTRAINDICATIONS

Brimonidine tartrate ophthalmic solution is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS

General: Although Brimonidine tartrate ophthalmic solution had minimal effect on blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

Brimonidine tartrate ophthalmic solution has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Brimonidine tartrate ophthalmic solution should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

During the studies there was a loss of effect in some patients. The IOP-lowering efficacy observed with Brimonidine tartrate ophthalmic solution during the first month of therapy may not always reflect the long-term level of IOP reduction. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients: The preservative in Brimonidine tartrate ophthalmic solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling Brimonidine tartrate ophthalmic solution to insert soft contact lenses.

As with other drugs in this class, Brimonidine tartrate ophthalmic solution may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Drug interactions: Although specific drug interaction studies have not been conducted with Brimonidine tartrate ophthalmic solution, the possibility of an additive or potentiating effect with

CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with Brimonidine tartrate ophthalmic solution in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after Brimonidine tartrate ophthalmic solution instillation are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, mutagenesis, impairment of fertility: No compound-related carcinogenic effects were observed in either mice or rats following a 21 month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved ~77 and 118 times, respectively, the plasma drug concentration estimated in humans treated with one drop Brimonidine tartrate ophthalmic solution into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberation assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility due to Brimonidine tartrate ophthalmic solution.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to Brimonidine tartrate ophthalmic solution. Dosing at this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Brimonidine tartrate ophthalmic solution should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50% - 83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

The safety and effectiveness of Brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years. (Also refer to Adverse Reactions section.)

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

Adverse events occurring in approximately 10-30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Events occurring in approximately 3-9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

The following events have been identified during post-marketing use of Brimonidine tartrate ophthalmic solution in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to Brimonidine tartrate ophthalmic solution, or a combination of these factors, include: bradycardia; hypotension; iritis; miosis; skin reactions (including erythema, eyelid pruritus, rash, and vasodilation); and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving Brimonidine tartrate ophthalmic solution.

OVERDOSAGE

No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of Brimonidine tartrate ophthalmic solution in the affected eye(s) three times daily, approximately 8 hours apart.

Brimonidine tartrate ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

HOW SUPPLIED

Brimonidine tartrate ophthalmic solution 0.2% is supplied sterile in white opaque LDPE plastic bottles and tips with purple high impact polystyrene (HIPS) caps as follows:

5 mL in 10 mL bottle NDC 60758-866-05
10 mL in 10 mL bottle NDC 60758-866-10
15 mL in 15 mL bottle NDC 60758-866-15

NOTE: Store between 15°-25°C (59°-77°F).

Rx only

Revised June 2002

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ab·o·li·tion·ary \-ə,nerē\ *adj* **:** relating to or favoring abolition

ab·o·li·tion·dom \-əndəm\ *n* -s **:** ABOLITIONISTS; *specif* **:** the northern states in the American Civil War

ab·o·li·tion·ism \-ə,nizəm\ *n* -s **:** the principles or measures favoring abolition (as of slavery or capital punishment) **:** the tenets or practices of abolitionists

ab·o·li·tion·ist \-ənəst\ *n* -s *often attrib* **:** an advocate of abolition

ab·o·li·tion·ize \-ə,nīz\ *vt* -ED/-ING/-S **:** to make abolitionists of (the members of a corporate body) ⟨~ Kansas⟩

abo·ma \əˈbōmə\ *n* -s [Pg, F, & AmerSp, prob. modif. of Kongo *mboma* python] **:** any of several large So. American snakes of the genus *Constrictor* or of related genera

ab·o·ma·sal \ˌabōˈmāsəl, -bə-\ *adj* [NL *abomasum* + E *-al*] **:** of, belonging to, or involving the abomasum

ab·o·ma·sum \,ˌˈsəm\ *also* **ab·o·ma·sus** \-səs\ *n, pl* **aboma·sa** \-sə\ *also* **aboma·si** \-,sī,-,sē\ [NL, fr. ¹*ab-* + L *omasum* tripe of a bullock] **:** the fourth or true digestive stomach of a ruminant

¹**a-bomb** \ˈā,-\ *n, usu cap A* [by abbr.] **:** ATOM BOMB

²**a-bomb** \"\ *vb, usu cap A* **:** ATOM-BOMB

a-bomber \ˈ-,--\ *n, usu cap A* **:** an aircraft capable of delivering a nuclear weapon (as an atom bomb) on a target

abom·i·na·ble \əˈbäm(ə)nəbəl\ *adj* [ME, fr. MF, fr. L *abominabilis*, fr. *abominari* + *-abilis* -able] **1 :** worthy of or causing loathing or hatred **:** revoltingly unnatural **:** DETESTABLE, LOATHSOME **2 :** quite disagreeable or unpleasant ⟨~ weather⟩ — **abom·i·na·bly** \-əblē, -i\ *adv*

abominable snowman *n, often cap A&S* [prob. intended as trans. of Tibetan *mi-te*, lit., man-bear] **:** an animal reported as existing in the high Himalayas and usu. thought to be a bear

¹**abom·i·nate** \əˈbämə,nāt, *usu* -ād·+V\ *vt* -ED/-ING/-S [L *abominatus*, past part. of *abominari* to deprecate as an ill omen, to detest, fr. *ab-* ¹ab- + *ominari* to forebode, presage, fr. *omin-, omen* omen] **:** to hate or loathe intensely **:** ABHOR ⟨~ a crime⟩ **syn** see HATE

²**abom·i·nate** \-mənət, -,nāt\ *adj* [L *abominatus*] **:** ABOMINATED

abom·i·na·tion \ə,bämə'nāshən\ *n* -s [ME *abominacioun*, fr. MF *abomination*, fr. LL *abomination-, abominatio*, fr. L *abominatus* + *-ion-, -io* -ion] **1 :** something that is abominable ⟨guilty of ~*s*⟩ ⟨a wonderful wooden statue . . . now replaced by the usual metal ~ —Norman Douglas⟩ **2 :** a feeling of extreme disgust and hatred **:** ABHORRENCE, DETESTATION, LOATHING ⟨tobacco . . . was held in ~ —T.B.Macaulay⟩

abom·i·na·tor \əˈbämə,nād·ə(r), -ātə-\ *n* -s **:** one that abominates

abon·go \əˈbäŋ(,)gō\ *n, pl* **abongo** *or* **abongos** *usu cap* **1 :** a Negrillo people on the Ogowe river, Gabon, French Equatorial Africa — called also *Obongo* **2 :** a member of the Abongo people — compare PYGMY

aboon \əˈbün, -ˈœn\ *adj or adv or prep* [ME *abone*, fr. earlier *aboven, abuven* — more at ABOVE] *chiefly dial* **:** ABOVE

ab·oospore \(ˈ)a'bōə,spō(ə)r\ *n* [¹*ab-* + *oospore*] **:** an oomycete spore functioning as an oospore but produced without sexual union

abor \ˈä,bō(ə)r\ *n, pl* **abor** *or* **abors** *usu cap* **1 :** a primitive people inhabiting the Brahmaputra river region about 100 miles north of the town of Dibrugarh in northern Assam **2 :** a member of the Abor people

ab·orad \(ˈ)aˈbōr,ad, -ō,r-\ *adv* [¹*ab-* + *orad*] **:** away from the mouth

ab·oral \(ˈ)aˈbōrəl, -ˈōr-,-ˈär-\ *adj* [¹*ab-* + *oral*] **:** opposite to or away from the mouth — **ab·oral·ly** \-əlē, -i\ *adv*

¹**abord** *vt* -ED/-ING/-S [ME *aborden*, fr. *abord*, adv., aboard — more at ABOARD] *archaic* **:** APPROACH, ACCOST

²**abord** *n* -s *archaic* **:** APPROACH **:** manner of approach

abordage *n* -s [¹*abord* + *-age*] *archaic* **:** boarding a ship in an attack

¹**ab·orig·i·nal** \ˌabəˈrijənᵊl, -jnəl\ *adj* [*aborigine* + *-al*] **1 a :** first according to historical record or scientific analysis **:** INDIGENOUS ⟨~ flora⟩ **b :** PRIMITIVE ⟨~ tribes⟩ ⟨a great safety valve for the ~ human impulses —Lewis Mumford⟩ **2 :** of or belonging to aborigines ⟨~ languages⟩ ⟨~ weapons⟩ **syn** see NATIVE

²**aboriginal** \"\ *n* -s **:** ABORIGINE

ab·orig·i·nal·i·ty \ˌabə,rijəˈnaləd·ē\ *n* -ES **:** the quality or state of being aboriginal

ab·orig·i·nal·ly \ˌ--ˈ-jənᵊlē, -jnəlē, -i\ *adv* **:** from the beginning **:** from earliest known times

ab·orig·i·ne \,abəˈrijə(,)nē, -əni\ *also* **ab·or·i·gen** \aˈbōrəjən, -ˈär-\ *n* -s [back-formation fr. *aborigines*, pl., fr. L, perh. irreg. fr. *ab origine* from the beginning] **1 :** an indigenous inhabitant of a country **:** one of the native people esp. as contrasted with an invading or colonizing people **2 aborigines** *pl* **:** the original fauna and flora of a geographical area

ab orig·i·ne \"\ *adv* [L] **:** from the beginning

abor-miri \ˌä,bōrˈmirē\ *n, usu cap A&M* **:** a language spoken in northern Assam

¹**aborn·ing** \əˈbōrniŋ, -ō(ə)n-, -nēŋ, -nən\ *adv* [¹*a-* + *borning*] **:** while being born or produced **:** at the moment of birth **:** before coming to completion — used esp. in the phrase *die aborning* ⟨a resolution that died ~⟩

²**aborning** \"\ *adj* **:** being born or produced ⟨the ~ social evolution of the girls —Fannie Hurst⟩ ⟨a new world was ~ overseas —B.D.Wolfe⟩

¹**abort** \əˈbō(ə)rt, -ō(ə)t, *usu* -d·+V\ *vb* -ED/-ING/-S [L *abortare*, fr. *abortus* abortion] *vi* **1 :** to bring forth premature or stillborn offspring ⟨cows with brucellosis often ~⟩ **2 :** to become checked in development so as to remain rudimentary or to shrink away ⟨pollen grains that ~⟩ **3 :** to stop or fail in the early stages ⟨many colds ~ without treatment⟩ ⟨the plans have ~*ed*⟩ ⟨the bomber ~*ed* from its mission⟩ ~ *vt* **1 :** to bring forth (offspring) prematurely ⟨~*ed* a 3-month-old fetus⟩ **:** cause to be delivered of a stillborn or nonviable fetus ⟨~ a malformed patient⟩; *esp* **:** to terminate pregnancy of before term **2 a :** to terminate prematurely ⟨~ a project⟩ **:** stop in the early stages ⟨~ a disease⟩ **b :** to turn back without completion **3 :** to check so as to produce rudimentary development or a shrinking away ⟨~ branches of trees⟩

²**abort** \"\ *n* -s [ME, fr. L *abortus*, fr. *abortus*, past part. of *aboriri* to disappear, miscarry, fr. *ab-* ¹ab- + *oriri* to rise, be born — more at ORIENT] **1** *obs* **:** ABORTION **2 :** an abortive flight by an aircraft on a combat or bombing mission; *also* **:** an aircraft making such a flight

abor·ti·cide \əˈbōrd·ə,sīd\ *n* -s [²*abort* + *-i-* + *-cide*] **1 :** act of destroying a fetus within the uterus **2 :** an agent that destroys the fetus and causes abortion

¹**abor·ti·fa·cient** \əˈbōrd·ə,fāshənt, ,-,--ˈ--\ *adj* [²*abort* + *-i-* + *-facient*] **:** inducing abortion

²**abortifacient** \"\ *n* -s **:** a drug or other agent that induces abortion

abort·in \əˈbōrtᵊn\ *n* -s [NL *abortus* (specific epithet of *Brucella abortus*, fr. L, past part.) + E *-in*] **:** an extract made from cultures of a bacterium (*Brucella abortus*) and used in the diagnosis of contagious abortion of cattle

abor·tion \əˈbōrshən, -ō(ə)sh-\ *n* -s [L *abortion-, abortio*, fr. *abortus* (past part.) + *-ion-, -io* -ion] **1 :** the expulsion of a nonviable fetus: **a :** spontaneous expulsion of a human fetus during the first 12 weeks of gestation — compare MISCARRIAGE **b :** induced expulsion of a human fetus **c :** expulsion often due to infection of a fetus by a domestic animal at any time before completion of pregnancy — see CONTAGIOUS ABORTION, VIBRIONIC ABORTION; TRICHOMONIASIS **2 a :** a misshapen thing or person **:** MONSTROSITY **3 :** something that fails to attain full development or that ceases to progress before it is matured or perfect ⟨his attempt proved an ~⟩ **4 a :** arrest of development of an organ so that it remains imperfect or is absorbed **b :** the result of such arrest of development (as a fruit that fails to reach maturity or a potential leaf reduced to a scale) **5 :** the arrest of a disease in its earliest stage ⟨~ of a cold⟩

abor·tion·ist \-nəst\ *n* -s **:** one who induces abortions esp. illegally

¹**abort·ive** \əˈbōr|d·iv, -ō(ə)|, |tiv, -ēv\ *adj* [ME, fr. L *abortivus*, fr. *abortus* (past part.) ...] **:** ... ⟨an ~ case of poliomyelitis⟩ — **abort·ive·ly** \-əvlē, -li\ *adv* — **abortiveness** \-ivnəs, -ēv-\ *n*

²**abortive** \"\ *n* -s [ME, fr. L *abortivus*, adj.] **:** one that is abortive (as a bombing mission)

abor·to·gen·ic \əˌbōrd·əˈjenik\ *adj* [²*abort* + *-o-* + *-genic*] **:** causing abortion **:** ABORTIFACIENT ⟨~ necrosis⟩

abor·tus \əˈbōrd·əs\ *n* -ES [NL, fr. L, abortion] **:** an aborted fetus; *specif* **:** a human fetus less than 12 weeks old or weighing at birth less than 17 ounces

abos *pl of* ABO

abo system \ˌāˌbēˈō-, ˌabēˈō-\ *n, usu cap A&B&O* **:** the basic system of antigens of human blood behaving in heredity as an allelic unit to produce any of the four blood groups A, B, AB, or O according to the particular antigens passed from parents to child — called also *ABO group*; compare ISOANTIBODY, RH FACTOR

à bouche \äbüsh\ *adj* [F, with a bouche] *heraldry, of a shield* **:** having a bouche on the dexter side

abought *past of* ABY

aboulia *var of* ABULIA

abound \əˈbau̇nd\ *vi* -ED/-ING/-S [ME *abounden*, fr. MF *abonder*, fr. L *abundare* to abound, overflow, fr. *ab-* ¹ab- + *undare* to rise in waves, fr. *unda* wave — more at WATER] **1 :** to be present or available in large numbers or in great quantity ⟨wild animals ~⟩ ⟨iron ore ~*s*⟩ ⟨~*ing* confidence⟩ **2 a** *obs* **:** to be wealthy ⟨feed the poor while he ~*s*⟩ **b :** to be full to overflowing ⟨~*ing* streams⟩ **c :** to be highly productive ⟨~*ing* soil⟩ **3 :** to become copiously supplied — used with *in* or *with* ⟨the city ~*s* in historic remains⟩ ⟨the fields ~ with stones⟩

¹**about** \əˈbau̇t, *usu* -d·+V\ *adv* [ME *about, abouten*, fr. OE *abūtan*, fr. ¹*a-* + *būtan* outside, without — more at BUT] **1 :** on all sides **:** in every direction **:** AROUND ⟨'tis time to look ~ —Shak.⟩ **2 a :** in rotation **:** ROUND ⟨they go ~ in circles⟩ **b :** around the outside **:** in circumference ⟨the lake is a mile ~ and a half mile across⟩ **c :** in a circuitous way **:** round about ⟨the river . . . is subject to frequent shifts of position, and winds ~ —P.E. James⟩ **3 a :** with some approach to exactness in quantity, number, or time **:** APPROXIMATELY ⟨~ four feet of snow⟩ ⟨~ eight o'clock⟩ **b :** ALMOST **:** NEARLY ⟨~ as serious⟩ **:** little less than ⟨~ starved⟩ **4 :** here and there at random ⟨tools lying ~⟩ **:** from one place to another ⟨carry money ~ with him⟩ **5 :** in the vicinity **:** NEAR ⟨he spoke to the people standing ~⟩ **6 :** in succession **:** one after the other **:** ALTERNATELY ⟨turn ~ is fair play⟩ **7 a :** in the opposite direction ⟨face ~⟩ ⟨bring a ship ~⟩ **:** in reverse order ⟨arranged the other way ~⟩ **:** from the contrary point of view ⟨put the matter the other way ~⟩ **b :** on the opposite tack — see COME ABOUT

²**about** \"\ *prep* [ME, fr. OE *abūtan*, fr. *abūtan*, adv.] **1 :** in a circle around **:** AROUND ⟨our thoughts revolve ~ ourselves⟩ **:** on every side of ⟨he found ~ him innumerable flowers⟩ **2 a :** in the immediate neighborhood of **:** NEAR ⟨fish are abundant ~ the reefs⟩ **b :** near or not far from in time ⟨a night ~ midsummer⟩ **c :** by or on (one's person) ⟨secreting money ~ him⟩ **d :** in or as a part of the makeup of ⟨a mature wisdom ~ him⟩ **e :** at the command of **:** in readiness for the use of ⟨he has his wits ~ him⟩ **3 a :** in the act or process of doing **:** engaged in ⟨I put it in the form of a poem while I was ~ it —Eudora Welty⟩ **:** concerned with ⟨no idea of what American music is ~⟩ **b :** on the point or verge of — usu. used with following infinitive ⟨~ to enter the army⟩ ⟨~ to be graduated⟩ **4 a** — used as a function word to indicate that which is dealt with as the object of thought, feeling, or action ⟨resentment ~ this state of affairs⟩ or that to which reference is made ⟨the most exciting thing ~ the adventure⟩ **b :** with regard to **:** CONCERNING **c :** on the subject of ⟨a novel ~ Spain⟩ **5 :** over or in different parts of ⟨he traveled ~ the country⟩ **:** THROUGHOUT ⟨a well-known figure ~ the town⟩ **:** here and there upon ⟨the knife wounded him ~ the face and throat⟩

³**about** \"\ *adj* [ME, fr. *about*, adv.] **1 :** stirring or moving from place to place **:** ASTIR ⟨few people were ~ on the streets⟩ **2 :** being in evidence, in existence, or in circulation **:** ABROAD ⟨plenty of money ~⟩ ⟨more reason and less emotion ~ —Herbert Hoover⟩ **3 :** normally active or capable (as after a confining illness) ⟨eager to be up and ~ again⟩

¹**about-face** \-ˌ-ˈ-\ *n* -s [fr. the imper. phrase *about face*, fr. ¹*about* + *face*, v.] **1 :** the act of facing in the opposite direction as a military maneuver ⟨soldiers did an *about-face* and marched away —Dorothy C. Fisher⟩ **2 a :** a reversal of direction ⟨the river does an *about-face*⟩ **b :** a reversal of attitude or point of view ⟨an *about-face* on national policies⟩

²**about-face** \"\ *vi* -ED/-ING/-S **:** to execute an about-face

about ship *vi* [fr. the imper. phrase *about ship*, fr. ¹*about* + *ship*, n.] **:** TACK — usu. used as an order

about-turn \-ˌ-ˈ-\ *vi* [fr. the imper. phrase *about turn*, fr. ¹*about* + *turn*, v.] **:** ABOUT-FACE

¹**above** \əˈbəv\ *adv* [ME *above, aboven*, fr. OE *abufan*, fr. ¹*a-* + *bufan* above (akin to OS *bi-oban*, MD *bōven*, OFris *bova*, MHG *bobene*), fr. *be-* + *ufan* above — more at OVER] **1 a :** in a higher place **:** OVERHEAD ⟨he lay under the tree and looked at the branches ~⟩ **:** in the sky ⟨the stars ~⟩ **:** in or to heaven ⟨gone ~⟩ **:** UPSTAIRS ⟨a stairway leading ~⟩ **b :** farther up (as on a mountain or river) ⟨the bridge is two miles ~⟩ **c :** on the upper or dorsal surface ⟨these young birds are light brown ~⟩ **2 :** higher on the same page or on a preceding page ⟨except as stated ~⟩ **3 :** higher or superior in rank, position, or power ⟨a vacancy in the rank ~⟩ **:** higher in number ⟨50 and ~⟩ **4** *archaic* **:** in addition **:** BESIDES

²**above** \"\ *prep* [ME *above, aboven*, fr. *above, aboven*, adv.] **1 a :** in or to a higher place than ⟨the house perched ~ the road⟩ **:** directly over ⟨a room ~ the store⟩ **:** higher than **b :** farther up than (as on a mountain or river) ⟨anchored 10 miles ~ the city⟩ **:** on the other side of **:** BEYOND ⟨hunted ~ the farm⟩ **c :** farther north than ⟨the ship sank just ~ the Azores⟩ **d :** on top of — used of clothing ⟨aprons ~ a motley of borrowed . . . raiment —Ellen Glasgow⟩ **2 a :** superior to or surpassing in any respect **:** higher than (as in rank, position, quality, or degree) ⟨filial piety is ~ self-interest⟩ **:** out of reach of **:** not likely to be affected by **:** not exposed to ⟨be ~ suspicion⟩ **:** in preference to **:** over against ⟨preoccupation with design ~ all other elements⟩ **b :** too proud or honorable to stoop or condescend to ⟨~ taking profits for himself⟩ **:** averse to **:** disinclined to ⟨she is not ~ reading her poems⟩ **3 :** exceeding in number, quantity, or size **:** more than ⟨men ~ 50 years old⟩ **4 :** in addition to **:** BESIDES ⟨~ and beyond his good nature⟩ — **above oneself :** showing or feeling self-importance ⟨when he gets a bit *above himself* . . . he inclines to be a nuisance —*Atlantic*⟩

³**above** \"\ *n* -s [ME *above, aboven*, fr. *above, aboven*, adv.] **1 a :** something that is located, written, or discussed higher on the same page or on a preceding page ⟨a diagram like the ~⟩ **b :** a person whose name is written higher on the same page or on a preceding page ⟨the ~ is the owner of this car⟩ **2 a :** higher esp. arbitrary authority ⟨the policy was imposed from ~⟩ **b :** HEAVEN ⟨every perfect gift is from ~ —Jas 1:17 (AV)⟩

⁴**above** \"\ *adj* [¹*above*] **1 :** being located, written, or discussed higher on the same page or on a preceding page ⟨the ~ chart⟩ **2 :** of heaven **:** HEAVENLY ⟨think on things ~⟩

above all *adv* **:** before every other consideration **:** ESPECIALLY ⟨this *above all*⟩

¹**above·board** \-ˌ-ˈ-\ *adv* [²*above* + *board*; fr. the difficulty of cheating at cards when the hands are above the table] **:** in a straightforward manner **:** OPENLY

²**aboveboard** \"\ *adj* **:** without concealment or deception **:** in open sight **:** STRAIGHTFORWARD ⟨open and ~ in his opposition⟩

above·ground \-ˌ-ˈ-\ *adj* **1 :** located on or above the surface of the grou...

above·proo...

¹**above·sta**... sat ~⟩

²**abovestai**... ıper

scoring of honors, penalties, and premiums — used of any score that does not count toward game; compare CONTRACT BRIDGE **2 :** classified as an ordinary or routine expense or revenue item or as a current expense or asset ⟨an *above-line* surplus⟩

above-wa·ter \-ˌ-ˈ-\ *adj* **1 :** above the surface of the water **2 :** above the waterline of a ship

ab ovo \(ˈ)aˈbō(,)vō\ *adv* [L, lit., from the egg] **:** from the beginning ⟨develops every thought *ab ovo*, leading the reader up to the finest ramifications —Arnold Brecht⟩

abox \əˈbäks\ *adj* [¹*a-* + *box* (to boxhaul)] **:** braced aback — used of head yards when the headsails only are aback

aboz·zo *also* **ab·boz·zo** \əˈbōt(,)sō\ *n, pl* **aboz·zi** \-(,)sē\ [It *abbozzo*, fr. *abbozzare* to make a rough sketch or draft, fr. *a-* (fr. L *ad-*) + *bozzare* to make a rough sketch or draft, fr. *bozza* boss, swelling, roughhewn stone, rough sketch or draft — more at BOSS] **:** a rough sketch or draft (as of a picture or a poem)

abp *abbr, often cap* archbishop

abr *abbr* abridged; abridgment

ab·ra·ca·dab·ra \ˌabrəkəˈdabrə\ *n* -s [LL] **1 :** a charm or incantation **:** magical formulas (relied on effigies and ~ to produce results —E.A. Hoebel) — used as a word to ward off calamity esp. when written on an amulet in a mystical design **2 :** confused or unintelligible language **:** JARGON, NONSENSE ⟨pseudoscientific ~⟩

A B R A C A D A B R A
A B R A C A D A B R
A B R A C A D A B
A B R A C A D A
A B R A C A D
A B R A C A
A B R A C
A B R A
A B R
A B
A

abracadabra

¹**abrad·ant** \əˈbrādᵊnt, aˈ-\ *n* -s [*abrade* + *-ant*] **:** ABRASIVE

²**abradant** \"\ *adj* **:** ABRASIVE

abrade \əˈbrād, aˈ-\ *vb* -ED/-ING/-S [L *abradere* to scrape off, fr. *ab-* ¹ab- + *radere* to scrape — more at RAT] *vt* **1 a :** to rub or wear away esp. by friction **:** ERODE ⟨the waves ~ the rocks⟩ **b :** to irritate by rubbing **:** CHAFE ⟨broad crape . . . *abraded* her soft skin —Arnold Bennett⟩ **c :** to roughen the surface of ⟨*abraded* yarns⟩ **2 :** to wear down or exhaust (as a person or a person's spirit) **:** IRRITATE ⟨the affront to his pride *abraded* him more and more —Robert Shaplen⟩ ~ *vi* **:** to undergo abrasion

abrad·er \-də(r)\ *n* -s **:** one that abrades ⟨a prod, scourge or ~ . . . of the local authorities —Keith Williams⟩: as **a :** a tool or machine for abrading **b** *or* **abrading stone** *archaeol* **:** a primitive stone artifact usu. of sandstone for smoothing, sharpening, or shaping

abra·ham-man \ˈābrə,ham,man, -haa(ə)m,maa(ə)n; ˈābrəm,-, ˈābrəhəm,-\ *also* **abram-man** \ˈābrəm,-\ *n, pl* **abra·ham-men** *also* **abram-men** *usu cap A* [after *Abraham* or *Abram*, Biblical patriarch of the Jews; prob. fr. the New Testament reference (Lk 16: 19–31) to the beggar Lazarus, who is said to have rested in Abraham's bosom after death] **:** one of a class of beggars who roamed through England esp. in the 16th and 17th centuries usu. feigning lunacy to obtain alms

abraham's bosom *n, usu cap A* [trans. of LL *sinus Abrahae*, trans. of Gk *kolpos Abraam*] **:** the abode of bliss in the other world **:** PARADISE — so called in Jewish writings and in the New Testament, in Lk 16:22 (RSV)

abram *obs var of* ¹AUBURN

ab·ra·mis \ˈabrəməs\ *n, cap* [NL, fr. Gk, a kind of mullet] **:** a genus of fishes (family Cyprinidae) including the European freshwater bream

abran·chia \(ˈ)āˈbraŋkēə\ *n pl, cap* [NL, fr. ²*a-* + *-branchia*] **:** a former division of annelids comprising forms without specialized respiratory structures (as most of the oligochaetes and leeches)

abran·chi·al \(ˈ)āˈbraŋkēəl\ *adj* [²*a-* + *branchial*] **:** ABRANCHIATE

abran·chi·al·ism \(ˈ)-ˈ---,lizəm\ *n* -s [*abranchial* + *-ism*] **:** the condition of being without gills (as certain mollusks of the genus *Firoloida*)

¹**abran·chi·a·ta** \ˌ-,-kēˈäd·ə, -ˈād·ə\ [NL, fr. ²*a-* + *branchi-* + *-ata*] *syn of* ABRANCHIA

²**abranchiata** \"\ *n pl, cap* **:** any of several groups of gill-less animals other than Abranchia

abran·chi·ate \(ˈ)-ˈ-kēət, -ē,āt\ *also* **abran·chi·ous** \-kēəs\ *adj* [²*a-* + *branchi-* + *-ate* or *-ous*] **:** lacking gills

abrase \əˈbrāz, aˈ-\ *vt* -ED/-ING/-S [L *abrasus*, past part. of *abradere* — more at ABRADE] **:** to wear down or rub off **:** smooth off **:** ABRADE

abras·er \-zə(r)\ *n* -s **:** ABRADER

abrash \ˈä,brəsh, -räsh\ *n* -ES [Ar, mottled] **:** a variation or deviation of a color in Oriental rugs

ab·ra·sin oil \ˈabrəzən-\ *n* [part trans. of F *huile d'abrasin*] **:** TUNG OIL

abra·si·om·e·ter \ə,brāzēˈäməd·ə(r), a,-\ *n* -s [*abrasion* + *-meter*] **:** a device for measuring the resistance of surfaces to abrasion

abra·sion \əˈbrāzhən, aˈ-\ *n* -s [ML *abrasion-, abrasio*, fr. L *abrasus* (past part. of *abradere* to scrape off) + *-ion-, -io* -ion — more at ABRADE] **1 :** wearing, grinding, or rubbing away by friction **2 a :** the rubbing or scraping of the surface layer of cells or tissue from an area of the skin or mucous membrane; *also* **:** a place so abraded **b :** the mechanical wearing away of the tooth surfaces by chewing

abrasion platform *n* **:** the portion of the submerged margin of a continent or island that has been planed off by marine abrasion as distinct from the portion that has been built up to its present level by the deposit of marine sediments

¹**abra·sive** \-āsiv, -ziv, -ēv\ *adj* [*abrase* + *-ive*] **1 :** tending to abrade **:** producing abrasion **2 :** causing irritation ⟨~ relationships between member nations⟩

²**abrasive** \"\ *n* -s **1 a :** any of a wide variety of natural or manufactured substances used to grind, wear down, rub away, smooth, scour, clean, or polish often combined with a binder to make grinding wheels or affixed with glue to the surface of paper or cloth **b :** something made of an abrasive (as sandpaper) **2 :** rock fragments, mineral particles, or sand grains used by running water, wind, waves and currents, and glaciers in abrading a land surface

ab·raum \ˈä,prau̇m\ *n* -s [G, lit., rubbish, fr. *ab* off (fr. OHG *aba* away) + *raum* space, fr. OHG *rūm* — more at OF, ROOM] **:** a red ocher used to darken mahogany

abrax·as \əˈbraksəs\ *n* [LL *Abraxas*, a god, fr. Gk *Abraxas*, *Abrasax*; perh. regarded as a charm fr. the numerical value of the Greek letters, which is 365] **1 —** used as a charm on an amulet or talisman in Europe, Asia Minor, and No. Africa from the 2d century B.C. until the 13th century **2** *also* **abraxas stone** -ES **:** a gem engraved with the word *abraxas*

abra·zo \əˈbrä(,)sō, äˈb-\ *n* -s [Sp, fr. *abrazar* to embrace, fr. *a-* (fr. L *ad-*) + *brazo* arm, fr. L *brachium* — more at BRACE] **:** an embrace (as of salutation) employed in Latin America

ab·re·act \ˌabrēˈakt\ *vt* -ED/-ING/-S [part trans. of G *abreagieren*, fr. *ab* off, away from, down from (fr. OHG *aba*) + *reagieren* to react — more at OF] **:** to release or express (an emotion previously repressed or forgotten) ⟨~ his resentment over a childhood slight⟩

ab·re·ac·tion \ˌabrēˈakshən\ *n* -s [part trans. of G *abreagierung*, fr. *ab* + *reagierung* reaction] **:** the discharge of the emotional energy supposed to be attached to a repressed idea esp. by the conscious verbalization of that idea in the presence of a therapist — compare CATHARSIS 3a

ab·re·ac·tive \-ktiv\ *adj* [*abreaction* + *-ive*] **:** relating to or capable of producing abreaction ⟨~ technique⟩

¹**abreast** \əˈ-\ *adv (or adj)* [ME *abrest*, fr. ¹*a-* + *brest* breast] **1 a :** beside one another with bodies in line ⟨four cars standing ~ so as to block the street⟩ ⟨with seats two ~ on each side of the aisle⟩ **b** *naut* **:** in or to a position with the bearing of another object 90 degrees from the bow **:** directly abeam ⟨~ of the tip of the island⟩ **2 :** up to or equal to a particular standard or level (as of performance or development) ⟨kept wages ...

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bois published in 1555 a systematic account of anatomy based on Galen's writings. He presented a relatively modern method of numbering branches of vessels, structures, and relationships. One of the structures described therein was the channel connecting the third and fourth ventricles of the brain; although his description was not original, the passage became known as the aqueduct of Sylvius, after Dubois's latinized professional name.

[1]aque·ous \ˈā-kwē-əs, ˈak-wē-\ *adj* **1 a :** of, relating to, or resembling water ⟨an ~ vapor⟩ **b :** made from, with, or by water ⟨an ~ solution⟩ **2 :** of or relating to the aqueous humor

[2]aqueous *n* : AQUEOUS HUMOR ⟨therapeutic release of ~ —*Physicians' Current Procedural Terminology*⟩

aqueous flare *n* : FLARE 3

aqueous humor *n* : a transparent fluid occupying the space between the crystalline lens and the cornea of the eye

aquos·i·ty \ə-ˈkwäs-ət-ē, ā-\ *n, pl* **-ties** : the quality or state of being moist or wet

Ar *symbol* argon

ara-A \ˌar-ə-ˈā\ *n* : VIDARABINE

ar·a·ban \ˈar-ə-ˌban\ *n* : a pentosan yielding arabinose on hydrolysis

arabic — see GUM ARABIC

arab·i·nose \ə-ˈrab-ə-ˌnōs, -ˌnōz\ *n* : a white crystalline aldose sugar $C_5H_{10}O_5$ occurring esp. in vegetable gums

ara·bi·no·side \ˌar-ə-ˈbin-ə-ˌsīd, ə-ˈrab-ə-nō-ˌsīd\ *n* : a glycoside that yields arabinose on hydrolysis

arab·i·tol \ə-ˈrab-ə-ˌtȯl, -ˌtōl\ *n* : a sweet crystalline alcohol $C_5H_7(OH)_5$ obtained by the reduction of arabinose

ar·a·chid·ic acid \ˌar-ə-ˌkid-ik-\ *n* : a white crystalline saturated fatty acid $C_{20}H_{40}O_2$ found in the form of esters esp. in vegetable fats and oils (as peanut oil)

ara·chid·o·nate \ˌar-ə-ˈkid-ᵊn-ˌāt\ *n* : a salt or ester of arachidonic acid

ar·a·chi·don·ic acid \ˌar-ə-kə-ˌdän-ik-\ *n* : a liquid unsaturated fatty acid $C_{20}H_{32}O_2$ that occurs in most animal fats, is a precursor of prostaglandins, and is considered essential in animal nutrition

ar·a·chis oil \ˈar-ə-kəs-\ *n* : PEANUT OIL

Arach·ni·da \ə-ˈrak-nəd-ə\ *n pl* : a large class of arthropods that are mostly air-breathing by means of trachea or book lungs, that include the spiders and scorpions, mites, and ticks, and that have a segmented body divided into two regions of which the anterior bears four pairs of legs but no antennae — **arach·nid** \-nəd\ *adj or n*

arach·nid·ism \-nə-ˌdiz-əm\ *n* : poisoning caused by the bite or sting of an arachnid (as a spider, tick, or scorpion); *esp* : a syndrome marked by extreme pain and muscular rigidity due to the bite of a black widow spider

ar·ach·ni·tis \ˌar-ˌak-ˈnīt-əs\ *n* : ARACHNOIDITIS

arach·no·dac·ty·ly \ə-ˌrak-nō-ˈdak-tə-lē\ *n, pl* **-lies** : a hereditary condition characterized esp. by excessive length of the fingers and toes — see CONGENITAL CONTRACTURAL ARACHNODACTYLY

[1]arach·noid \ə-ˈrak-ˌnȯid\ *n* : a thin membrane of the brain and spinal cord that lies between the dura mater and the pia mater

[2]arachnoid *also* **arach·noi·dal** \ə-ˌrak-ˈnȯid-ᵊl\ *adj* : of or relating to the arachnoid ⟨the ~ membrane⟩

arach·noi·dea \ə-ˌrak-ˈnȯid-ē-ə\ *n* : ARACHNOID

arachnoid granulation *n* : any of the small whitish processes that are enlarged villi of the arachnoid membrane of the brain which protrude into the superior sagittal sinus and into depressions in the neighboring bone — called also *arachnoid villus, pacchionian body*

arach·noid·ism \ə-ˈrak-ˌnȯid-ˌiz-əm\ *n* : ARACHNIDISM

arach·noid·itis \ə-ˌrak-ˌnȯid-ˈīt-əs\ *n* : inflammation of the arachnoid membrane

arachnoid villus *n* : ARACHNOID GRANULATION

arach·no·ly·sin \ə-ˌrak-nō-ˈlī-sᵊn\ *n* : a hemolysin secreted by some spiders

ara·lia \ə-ˈrā-lē-ə, -lyə\ *n* **1** *cap* : a large genus (family Araliaceae) of widely distributed often aromatic herbs, shrubs, and trees with compound leaves and umbellate flowers that includes some with medicinal properties **2 :** a plant of the genus *Aralia* **3 :** the dried rhizome and roots of the American spikenard (*Aralia racemosa*) used as a diaphoretic and aromatic

ar·a·ro·ba \ˌar-ə-ˈrō-bə\ *n* : GOA POWDER

ar·bor \ˈär-bər\ *n* : a branching anatomical structure resembling a tree

ar·bo·res·cent \ˌär-bə-ˈres-ᵊnt\ *adj* : resembling a tree in growth, structure, or appearance

ar·bo·ri·za·tion *or Brit* **ar·bo·ri·sa·tion** \ˌär-bə-rə-ˈzā-shən\ *n* : a treelike figure or arrangement of branching parts; *esp* : a treelike part or process (as a dendrite) of a nerve cell ⟨the terminal ~ of an axon⟩

ar·bo·rize *or Brit* **ar·bo·rise** \ˈär-bə-ˌrīz\ *vi* **-rized** *or Brit* **-rised; -riz·ing** *or Brit* **-ris·ing** : to branch freely and repeatedly ⟨the nerve fibers *arborized*⟩

ar·bo·vi·rol·o·gist \ˌär-bə-ˌvī-ˈräl-ə-jəst\ *n* : a specialist in arbovirology

ar·bo·vi·rol·o·gy \ˌär-bə-ˌvī-ˈräl-ə-jē\ *n, pl* **-gies** : a branch of virology that deals with the arboviruses

ar·bo·vi·rus \-ˈvī-rəs\ *n* : any of a group of RNA viruses (as the causative agents of encephalitis, yellow fever, and dengue) transmitted by arthropods

ar·bu·tin \ˈär-ˈbyüt-ᵊn, ˈär-byə-tən\ *n* : a crystalline glucoside $C_{12}H_{16}O_7$ found in the leaves of various plants (as the bearberry) of the heath family (Ericaceae) and sometimes used as a urinary antiseptic

Ar·bu·tus \är-ˈbyüt-əs\ *n* : a genus of shrubs and trees of the heath family (Ericaceae) having white or pink flowers and scarlet berries and including some from which arbutin is obtained

arc \ˈärk\ *n* **1 :** an arched or curved anatomical part, distance, or pathway — see REFLEX ARC **2 :** a sustained luminous discharge of electricity across a gap in a circuit or between electrodes

ARC *abbr* **1** AIDS-related complex **2** American Red Cross

ar·cade \är-ˈkād\ *n* **1 :** an anatomical structure comprising a series of arches **2 :** DENTAL ARCH

arch \ˈärch\ *n* **1 :** an anatomical structure that resembles an arch in form or function: as **a :** either of two vaulted portions of the bony structure of the foot that impart elasticity to it: (1) **:** a longitudinal arch supported posteriorly by the basal tuberosity of the calcaneus and anteriorly by the heads of the metatarsal bones (2) **:** a transverse arch consisting of the metatarsals and first row of tarsals and resulting from elevation of the central anterior portion of the median longitudinal arch **b :** ARCH OF THE AORTA **2 :** a fingerprint in which all the ridges run from side to side and make no backward turn

ar·cha·ic \är-ˈkā-ik\ *adj* **1 :** typical of a previously dominant evolutionary stage ⟨~ features of a fossil skull⟩ **2 :** having the characteristics of primitive humans and their animal forebears esp. as represented in the unconscious and appearing in behavior as manifestations of the unconscious

arch·en·ter·on \är-ˈkent-ə-ˌrän, -rən\ *n, pl* **-tera** \-ə-rə\ : the cavity of the gastrula of an embryo forming a primitive gut — called also *gastrocoel*

ar·che·spo·ri·um \ˌär-ki-ˈspōr-ē-əm, -ˈspȯr-\ *n, pl* **-spo·ria** \-ē-ə\ : the cell or group of cells from which spore mother cells develop — **ar·che·spo·ri·al** \ˌär-ki-ˈspōr-ē-əl, -ˈspȯr-\ *adj*

ar·che·type \ˈär-ki-ˌtīp\ *n* **1 a :** a primitive generalized plan of structure deduced from the characters of a natural group of plants or animals and assumed to be the characteristic of the ancestor from which they are all descended **b :** the original ancestor of a group of plants or animals **2 :** an inherited idea or mode of thought in the psychology of C. G. Jung that is derived from the experience of the race and is present in the unconscious of the individual — **ar·che·typ·al** \ˌär-ki-ˈtī-pəl\ *adj*

ar·chi·a·ter \ˈär-kē-ˌāt-ər, ˌär-kē-ˈ\ *n* : a chief physician

Hawley's

Condensed Chemical Dictionary

Fourteenth Edition

Revised by

Richard J. Lewis, Sr.

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This book is printed on acid-free paper. ∞

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Properties: Viscous, dark-brown liquid; unpleasant odor. D 0.78–0.97, flash p 20–90F.
Hazard: Flammable, moderate fire risk. Toxic by ingestion, local skin irritant. For further information refer to The American Petroleum Institute.
See natural gas; petrochemical; see Appendix E 4 for history of the industry.

petroleum benzin. A special grade of ligroin.

petroleum coke. See coke.

petroleum ether. This term is used synonymously with petroleum naphtha. It is also sometimes used as a synonym for ligroin or petroleum spirits. It is technically a misnomer, because it is not an ether in the chemical sense. For details about specified distillation ranges and other distinctive properties, consult ASTM and API specifications.
See naphtha (1).

petroleum gas, liquefied. See liquefied petroleum gas.

petroleum jelly. See petrolatum

petroleum naphtha. See naphtha (1).

petroleum spirits. In Great Britain the term *petroleum spirits* refers to a volatile hydrocarbon mixture having a flash p 32F (0C).
Hazard: Highly flammable, dangerous fire risk.
See naphtha (1a); spirits; petroleum ether.

petroleum, synthetic. See pyrolysis.

petroleum thinner. See naphtha (1a).

petroleum wax. A high molecular weight solid hydrocarbon derived from petroleum. There are three types: paraffin waxes, microcrystalline waxes, and petrolatum waxes. All are made mostly by solvent dewaxing, although pressing and sweating processes are still used.

"Petrolite" ***[Baker Petrolite].*** TM for a hard grade of petroleum microcrystalline wax; a synthetic polymer; an oxidized hydrocarbon; a modified hydrocarbon; or a despersion.

"Petromat" ***[Phillips].*** TM for engineered nonwoven fabric.
Use: Paving repair.

"Petronates" ***[Crompton & Knowles].*** TM for salts of petroleum sulfonic acids, varying in molecular weight and color.
Use: Emulsifying agents, dispersing agents, wetting agents, corrosion preventive.

"Petronauba" ***[Baker Petrolite].*** TM for an oxidized hydrocarbon.

"Petrotac" ***[Phillips].*** TM for engineered nonwoven fabric.
Use: Paving repair membranes.

"Petrothene" ***[Quantum].*** TM for polypropylene resins for blown, cast, and water-quenched films, substrate coating, wire and cable coating, injection molding, blow molding, thermoforming, pipe extrusion, calendering.
Available forms: Solid cubes and pellets in natural and black.

"Petrowet" R ***[Du Pont].*** TM for a surface-active agent composed of saturated hydrocarbon sodium sulfonate. A wetting and penetrating agent effective in high concentration of electrolytes and acids, suitable for use in acidizing of oil wells.

pewter. Tin alloys with 5–15% tin, 0–3% copper, and 0–15% lead. White metal and Britannia metal are also of this general composition.

peyote. Root of cactus *Lophophora williamsii* (Mexico) known as an hallucinogen.

PF resins. Abbreviation for phenol-formaldehyde resins.

Pfau-Plattner azulene synthesis. Formation of azulenes by ring enlargement of indanes on addition of diazoacetic ester, hydrolysis, dehydrogenation, and decarboxylation of the resulting acid.

Pfitzinger reaction. Formation of quinoline-4-carboxylic acids by condensation of isatic acids from isatin with α-methylene carbonyl compounds; subsequent decarboxylation yields quinolines.

Pfitzner-Moffatt oxidation. Oxidation of alcohols to carbonyl derivatives with dimethyl sulfoxide and dicyclohexylcarbodiimide. The procedure is especially useful for the conversion of a primary alcohol to an aldehyde without further oxidation to the carboxylic acid.

PG. Abbreviation for polypropylene glycol.

PGA. Abbreviation for pteroylglutamic acid.
See folic acid.

PGDN. See propylene glycol dinitrate.

pH. pH is a value taken to represent the acidity or alkalinity of an aqueous solution; it is defined as the logarithm of the reciprocal of the hydrogen-ion concentration of a solution:

$$pH = \log_{10} \frac{1}{[H^+]}$$

The pH scale is designed to conveniently characterize the acidity of aqueous acid-base systems. Pure water is the standard used for the pH scale. Under ordinary conditions water molecules dissociate into the ions H^+ and OH^-, with recombination at such a rate that with very pure water at 22C there is a concentration of oppositely charged ions of 1/10,000,000, or 10^{-7}, mole per liter. This is commonly expressed by saying that pure water has a pH of 7, which means that its concentration of hydrogen ions is expressed by the exponent 7, without its minus sign. When acids or hydroxyl-containing bases are in water solution they ionize more or less completely, furnishing varying concentrations of H^+ and OH^- ions, respectively, to the solution. Strong acids and bases ionize much more completely than weak acids and bases; thus strong acids give solutions of pH 1–3, while solutions of weak acids have a pH of 6. Strong bases give solutions of pH 12 or 13, while weak bases give solutions of pH 8. Because the pH scale is logarithmic, the intervals are exponential and thus represent far greater differences in concentration than the values themselves seem to indicate (see table).

	pH Value	Ratio of H^+ or OH^- Concentration to That of Pure Water at 22C
Acid side (excess of H^+ ions)	1	1,000,000
	2	100,000
	3	10,000
	4	1,000
	5	100
	6	10
Neutrality	7	1
Alkaline side (excess of OH^- ions)	8	10
	9	100
	10	1,000
	11	10,000
	12	100,000
	13	1,000,000

Liquid	pH Value
Pure water	7
Seawater	7.8–8.2
Electroplating bath	6.5–5
0.01 *N* HCl	2
0.1 *N* HCl	1.08
0.1 *N* H_2SO_4	1.17
0.01 *N* NaOH	12
0.1 *N* acetic acid	3
0.1 *N* NH_4OH	11
Gastric juices	1.7
Urine	5–7
Blood	7.3–7.5
Milk	6.5–7
Soil (optimum for crops)	6–7

In acid-base titrations, changes in pH can be detected by indicators such as methyl orange, phenolphthalein, etc. Litmus paper can also be used as a rough indication of acidity or alkalinity. In carrying out titrations, the end point signaled by an indicator does not always correspond to a neutral pH (7). pH control is of critical importance in a large number of industrial operations such as water purification, chrome tanning process for leather, in preservation of food products, in electroplating baths, dyeing, agriculture, and numerous other instances.
See acid; base.

phaltan. See folpet.

pharaoh's serpent eggs. (mercuric thiocyanate). $(NCS)_2Hg$. Swells when heated.

pharmaceutical. A broad term that includes not only all types of drugs and medicinal and curative products but also ancillary products such as tonics, dietary supplements, vitamins, deodorants, and the like.
See drug.

"Pharmolin" ***[Engelhard].*** (kaolin clay). TM for aluminum silicate.
Use: For various internal and external pharmaceutical compositions used in antidiarrheal medications.

phase. (1) One of the three states or conditions in which substances can exist, i.e., solid, liquid, or gas (vapor). The condition depends primarily on the concentration of atoms of molecules; solids are the most dense, gases the least, and liquids occupy the intermediate position. Solids are normally crystals, liquids are amorphous, and gases are without structure.
See matter. (2) A physically distinct and mechanically separable portion of a dispersion or solution. Phases may be solid, liquid, or gaseous (vapor). In any mixture or solution the major component is called the continuous or external phase and the minor component the dispersed or internal phase. The latter may or may not be uniformly dispersed in the continuous phase.
See colloid chemistry; solution.

phase rule. Propounded by J. Willard Gibbs in 1877, the phase rule is a general system of equations of the form $F = C - P + 2$ stating the boundaries of thermodynamic equilibrium in a system of chemical reactants. The number of degrees of freedom (F) allowed in a given heterogeneous system may be examined by analysis or observation and plotted on a graph by proper choice of the components (C), the phases (P), and the independently variable factors of temperature and pressure. The principles of the phase rule apply to all multicomponent systems, including solvent blends, glass, alloys, and plastics.